(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 August 2005 (18.08.2005)

PCT

(10) International Publication Number
WO 2005/075480 A1

(51) International Patent Classification[7]: C07D 487/04, 417/12, 417/04, 277/34, A61K 31/4188, 31/427

(21) International Application Number: PCT/EP2005/000840

(22) International Filing Date: 28 January 2005 (28.01.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P 200400205 30 January 2004 (30.01.2004) ES

(71) Applicant *(for all designated States except US)*: **CEPA SCHWARZ PHARMA S.L.** [ES/ES]; Paseo de la Castellana 141, E-28046 Madrid (ES).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LOPEZ RODRIGUEZ, Maria, Luz** [ES/ES]; Rector Royo Villanova 10, E-28040 Madrid (ES). **BENHAMU SALAMA, Bellinda** [ES/ES]; Valdeparra 76, E-28100 Alcobendas, Madrid (ES). **DEL RIO ZAMBRANA, Joaquin** [ES/ES]; Irunlarrea 13, E-31008 Pamplona, Navarra (ES). **FRECHILLA MANSO, Diana** [ES/ES]; Amaya 24, E-31004 Pamplona, Navarra (ES). **MARCO MARTINEZ, Isabel** [ES/ES]; Pedro Rico 11, E-28029 Madrid (ES).

(74) Agents: **DE JUSTO, V., Jorge** et al.; c/o Jacobacci & Partners, M. & J. de Justo, Castellana 128, E-28046 Madrid (ES).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/075480 A1

(54) Title: DIAZA- OR THIAZADIONE DERIVATIVES WITH NEUROPROTECTIVE ACTIVITY

(57) Abstract: The present invention relates to certain derivatives of cycloalkanediones invariably substituted with a chroman-2-yl, 2-quinolyl or -O-phenyl residue which are serotonin (5-hydroxytryptamine, 5-HT) 5-HT_{1A} receptor subtype agonists modulators, to their stereochemical isomers and to their use in the preparation of a medicament for the treatment of pathological states for which an agonist a modulator of these receptors is indicated.

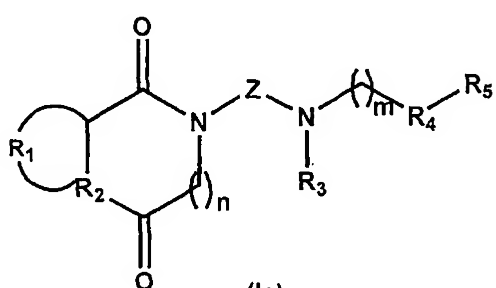
DIAZA- OR THIAZHADIONE DERIVATIVES WITH WITH NEUROPROTECTIVE ACTIVITY

FIELD OF THE INVENTION

The present invention relates to certain derivatives of cycloalkanediones invariably substituted with a chroman-2-yl, 2-quinolyl or –O-phenyl residue which are serotonin (5-hydroxytryptamine, 5-HT) 5-HT_{1A} receptor subtype agonists modulators, to their stereochemical isomers and to their use in the preparation of a medicament for the treatment of pathological states for which an agonist a modulator of these receptors is indicated.

BACKGROUND OF THE INVENTION

PCT/ES03/00394 discloses cycloalkanedione derivatives of general formula Ia:



(Ia)

wherein:

R_1 is selected from the group formed by H, -$(CH_2)_3$-, -$(CH_2)_4$-, -CH_2-S-CH_2, -S-CH_2-CH_2-;

R_2 is selected from the group formed by N, S;

n has a value of 0 or 1;

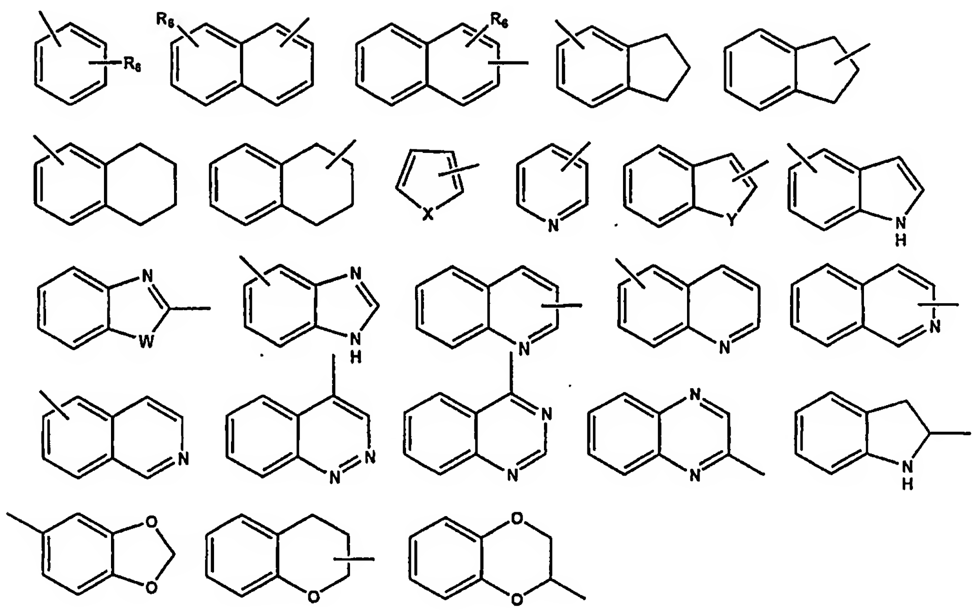
Z is selected from the group formed by C_2-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkinyl;

R_3 is selected from the group formed by H, C_1-C_{10}-alkyl, aryl, aralkyl;

m has a value of 0 to 2;

R_4 is selected from the group formed by O, CH_2;

R_5 is selected from the group formed by:



wherein:

R_6 is selected from the group formed by H, C_1-C_5-alkyl, C_1-C_5-alkoxy, OH, F, Cl, Br, I;

X is selected from the group formed by O, S, NH, NCH_3;

Y is selected from the group formed by O, NH;

W is selected from the group formed by S, NH.

PCT/ES03/00394 describes radioligand displacement tests to characterize the <u>in vitro</u> affinity and selectivity in the 5-HT_{1A} cerebral receptors of some of the possible compounds represented by the previous Markush formula (Ia), whilst the functional character (agonist / antagonist) was determined by the study of their effect on adenylate cyclase in HeLa cells transfected with the human 5-HT_{1A} receptor, measuring their inhibiting effect on the stimulation of the enzyme induced by forskolin for the compounds:

- 2-[4-[(Chroman-2-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, (a)
- 2-[4-[(Chroman-2-yl)methylamino]butyl]-1,3-dioxoperhydroimidazo[1,5-*b*]thiazole, (b)
- 2-[4-[(Chroman-2-yl)methylamino]butyl]-1,3-dioxoperhydroimidazo[1,5-*c*]thiazole, (c)
- 3-[4-[(Chroman-2-yl)methylamino]butyl]-2,4-dioxothiazolidine, (d)

- 2-[4-[2-(Phenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, (e)

For these compounds (a, b, c, d, e), an in vivo functional characterization test was performed by the quantification of the hypothermia associated to the stimulation of the receptor. Furthermore, the neuroprotective effect was evaluated by in vitro experimental models using primary cultures of rat hippocampus exposed to serum deprivation (compounds a, d, and e), to a toxic concentration of glutamate (compound a), or incubated in conditions of hypoxia and absence of glucose (compound a). On the other hand, the determination of the in vivo neuroprotective action is evaluated both in the transient global ischemia model in gerbils (compounds a and e) and in the permanent focal ischemia model in rats (compound a).

SUMMARY OF THE INVENTION

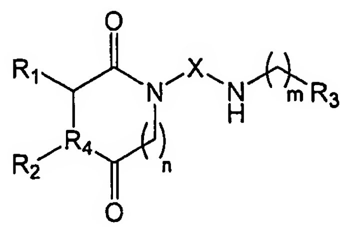
The present invention relates to a group of cycloalkanedione derivatives which are invariably substituted with a chroman-2-yl residue, a 2-quinolyl residue or an –O-phenyl residue.

In extensive studies the inventors have surprisingly identified a class of compounds with a high affinity for the $5\text{-}HT_{1A}$ receptor and remarkable neuroprotective properties.

The $5\text{-}HT_{1A}$ affinity has been demonstrated by in vitro radioligand displacement tests. Likewise, their affinity for the serotonergic $5\text{-}HT_{2A}$, $5\text{-}HT_3$, $5\text{-}HT_4$ and $5\text{-}HT_7$ receptors, 5-HT transporter, adrenergic α_1 and dopaminergic D_2 receptors have been characterized. The functional character (agonist/antagonist) of the new ligands was studied, determining the inhibition of the stimulating effect of forskolin on adenylate cyclase and studying, furthermore, in vivo, the $5\text{-}HT_{1A}$ agonist character of the new compounds by hypothermia analysis. In the same way, the compounds of the present invention have shown in vitro neuroprotective action on primary cultures of rat hippocampus, considering those models of neuronal death (deprivation of trophic factors and deprivation of oxygen and glucose) wherein the serotonergic $5\text{-}HT_{1A}$ agonists are more effective. The protective effect was also studied for cerebral infarction induced by permanent occlusion in the middle cerebral artery

in rats.

According to a first aspect of the present invention, it relates to compounds of the general formula I:



their stereochemically isomer forms, hydrates, solvates and pharmaceutically acceptable salts thereof, wherein:

R_1 and R_2 are H or are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring; if R_4=S then R_1 is H and R_2 is absent;
R_4 is selected from the group consisting of N and S;
n being an integrer from 0 to 1;
X is selected from the group consisting of C_2-C_{10}-alkyl, C_2-C_{10}-alkenyl and -CH_2-Y-CH_2-; wherein Y is phenyl;
m being an integrer from 1 to 2;
R_3 is selected from the group consisting of chroman-2-yl, 2-quinolyl and -O-phenyl, wherein the aromatic ring of the chromanyl moiety, the quinolyl or the phenyl residue is optionally substituted by one or more groups chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, halogen, C_2-C_6-alkenyl, halo-(C_1-C_6)-alkyl, halo-(C_1-C_6)-alkoxy, phenyl, phenyl(C_1-C_6)-alkyl, phenoxy, C_1-C_6-alkylcarbonyl, phenylcarbonyl, phenyl(C_1-C_6)alkylcarbonyl, C_1-C_6-alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, C_1-C_6-alkylcarbonylamino, hydroxy, cyano, nitro, amino, N-(C_1-C_6)-alkylamino, N,N-(C_1-C_6)-dialkylamino, carboxy, sulfo, sulfamoyl, sulfonylamino, (C_1-C_6)alkylaminosulfonyl or (C_1-C_6)alkylsulfonylamino; or wherein the phenyl ring is substituted by two neighbouring residues, which together with the phenyl ring to which they are attached form tetrahydronaphthyl; wherein each alkyl is optionally substituted with hydroxy or amino;
provided that the compound is not 2-[4-[(chroman-2-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, 3-[4-[(chroman-2-yl)methylamino]butyl]-2,4-dioxothiazolidine, 3-[5-[(chroman-2-yl)methylamino]pentyl]-2,4-

dioxothiazolidine, 3-[6-[(chroman-2-yl)methylamino]hexyl]-2,4-dioxothiazolidine, 2-[4-[2-(phenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole or 3-[4-[2-(phenoxy)ethylamino]butyl]-2,4-dioxothiazolidine.

In a preferred embodiment, R_3 is preferably selected from the group consisting of chroman-2-yl, 2-quinolyl and -O-phenyl, wherein the phenyl residue is optionally substituted by a group chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, or halogen.

The present invention comprises three main embodiments:

(1) m is 1 and R_3 is optionally substituted chroman-2-yl
(2) m is 2 and R_3 is optionally substituted O-phenyl
(3) m is 1 and R_3 is optionally substituted 2-quinolyl

According to a first preferred main embodiment of the present invention, m is 1 and R_3 is chroman-2-yl, the phenyl ring of which is unsubstituted or substituted by one or more groups chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, halogen, C_2-C_6-alkenyl, halo-(C_1-C_6)-alkyl, halo-(C_1-C_6)-alkoxy, phenyl, phenyl(C_1-C_6)-alkyl, phenoxy, C_1-C_6-alkylcarbonyl, phenylcarbonyl, phenyl(C_1-C_6)alkylcarbonyl, C_1-C_6-alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, C_1-C_6-alkylcarbonylamino, hydroxy, cyano, nitro, amino, N-(C_1-C_6)-alkylamino, N,N-(C_1-C_6)-dialkylamino, carboxy, sulfo, sulfamoyl, sulfonylamino, (C_1-C_6)alkylaminosulfonylor (C_1-C_6)alkylsulfonylamino; wherein each alkyl is optionally substituted with hydroxy or amino. R_3 is preferably unsubstituted chroman-2-yl.

Unless specifically mentioned otherwise the term "chroman-2-yl" refers to an unsubstituted chroman-2-yl residue.

According to a first embodiment of this first preferred main embodiment of the invention, R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring and R_4 is N.

Those compounds wherein m is 1 and R_3 is chroman-2-yl, R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5- or 6-membered ring; R_4 is N; and X is selected from the group consisting of C_2-C_{10}-

alkyl, (*E*)-2-butenyl, 3-methylbenzyl or 4-methylbenzyl are preferred.

In a second embodiment of this first preferred main embodiment of the present invention, R_1 is H; R_2 is absent; R_4 is S; m is 1; R_3 is chroman-2-yl; and X is selected from the group consisting of C_2-C_{10}-alkyl, C_2-C_{10}-alkenyl, or -CH_2-Y-CH_2-, wherein Y is phenyl. In one embodiment n is preferably 0.

In a more preferred embodiment of the present invention, it provides compounds of formula (I) wherein: R_1 is H; R_2 is absent; R_4 is S; m is 1; R_3 is chroman-2-yl; and X is C_2-C_{10}-alkyl. In one embodiment n is preferably 0.

A second preferred main embodiment of the invention relates to compounds wherein m is 2 and R_3 is –O-phenyl optionally substituted by one or more groups chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, halogen, C_2-C_6-alkenyl, halo-(C_1-C_6)-alkyl, halo-(C_1-C_6)-alkoxy, phenyl, phenyl(C_1-C_6)-alkyl, phenoxy, C_1-C_6-alkylcarbonyl, phenylcarbonyl, phenyl(C_1-C_6)alkylcarbonyl, C_1-C_6-alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, C_1-C_6-alkylcarbonylamino, hydroxy, cyano, nitro, amino, N-(C_1-C_6)-alkylamino, N,N-(C_1-C_6)-dialkylamino, carboxy, sulfo, sulfamoyl, sulfonylamino, (C_1-C_6)alkylaminosulfonyl or (C_1-C_6)alkylsulfonylamino; or wherein the phenyl ring is substituted by two neighbouring residues, which together with the phenyl ring to which they are attached form tetrahydronaphthyl; wherein each alkyl is optionally substituted with hydroxy or amino.

According to a more preferred embodiment of the second main embodiment of the invention, it relates to compounds of formula (I) wherein: m=2 and R_3 is –O-phenyl, wherein the phenyl ring is substituted by one or more groups chosen from phenyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkoxy, C_1-C_6-alkyl, halo-(C_1-C_6)-alkyl, or halogen or wherein the phenyl group is substituted by two neighbouring residues, which together with the phenyl group to which they are attached form tetrahydronaphthyl.

In another preferred embodiment, m=2 and R_3 is –O-phenyl, wherein the phenyl ring is substituted by one or more groups chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, or halogen.

Most preferred compounds are those wherein the phenyl residue is

optionally substituted by one or more groups chosen from methoxy, ethoxy, propoxy, isopropoxy, ethyl, propyl, isopropyl, bromide, trifluoromethyl, methylamide or ethoxycarbonyl.

Particularly preferred are those compounds wherein the phenyl residue is substituted in *ortho* and/or *meta* position.

According to a preferred embodiment of this second preferred embodiment of the invention, R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring; and R_4 is N.

Particularly preferred compounds are those wherein R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5-membered ring; R_4 is N; n is 0; X is C_2-C_{10}-alkyl; m is 2; R_3 is –O-phenyl optionally substituted by one or more groups chosen from phenyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylcarbonylamino, C_1-C_6-alkoxy, C_1-C_6-alkyl, halo-(C_1-C_6)-alkyl, or halogen or wherein the phenyl group is substituted by two neighbouring residues, which together with the phenyl group to which they are attached form tetrahydronaphthyl.

In a more specific embodiment R_3 is O-phenyl substituted by a group chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, or halogen.

In another preferred embodiment of this second preferred main embodiment of the invention, R_1 is H, R_2 is absent and R_4 is S. Particularly those wherein X is C_2-C_{10}-alkyl and n is 0.

According to a third main embodiment of the present invention, it relates to compounds of formula (I) wherein m is 1 and R_3 is 2-quinolyl, the aromatic ring of which is unsubstituted or substituted by one or more groups chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, halogen, C_2-C_6-alkenyl, halo-(C_1-C_6)-alkyl, halo-(C_1-C_6)-alkoxy, phenyl, phenyl(C_1-C_6)-alkyl, phenoxy, C_1-C_6-alkylcarbonyl, phenylcarbonyl, phenyl(C_1-C_6)alkylcarbonyl, C_1-C_6-alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, C_1-C_6-alkylcarbonylamino, hydroxy, cyano, nitro, amino, N-(C_1-C_6)-alkylamino, N,N-(C_1-C_6)-dialkylamino, carboxy, sulfo, sulfamoyl, sulfonylamino, (C_1-C_6)alkylaminosulfonyl or (C_1-C_6)alkylsulfonylamino; wherein each alkyl is optionally substituted with hydroxy or amino. R_3 is preferably

unsubstituted 2-quinolyl.

Unless specifically mentioned otherwise the term “2-quinolyl” refers to an unsubstituted quinolyl residue.

In a preferred embodiment of this third preferred main embodiment of the invention, R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring; and R_4 is N. Those compounds wherein n is 0; and X is C_2-C_{10}-alkyl are particularly preferred.

In the context of the present invention, the term "alkyl" relates to a saturated, linear or branched hydrocarbon chain. The “alkyl”-group may be unsubstituted or substituted. “Alkyl” is preferably unsubstituted. If the “alkyl” group (also as a part of e.g. phenylalkyl, alkylcarbonyl or alkoxy) is substituted, the substituents are preferably hydroxyl or amino. Unless specifically mentioned otherwise, the term “alkyl” refers to an unsubstituted hydrocarbon chain.

In the context of the present invention, the term "C_2-C_{10}-alkyl" relates to a saturated, linear or branched hydrocarbon chain, that contains from 2 to 10 carbon atoms. The term "C_2-C_{10}-alkenyl" relates to a linear or branched hydrocarbon chain that contains from 2 to 10 carbon atoms and which has at least one double bond.

The term "C_1-C_6-alkyl" relates to a saturated, linear or branched hydrocarbon chain that contains from 1 to 6 carbon atoms.

The term “halogen”, as used in this specification, consisting of fluorine, chloride, bromide, and iodine.

The term “halo-(C_1-C_6)-alkyl” refers to “C_1-C_6 alkyl” as defined above, which is substituted with at least one halogen atom. It includes as preferred embodiments difluoromethyl and trifluoromethyl.

The term “(C_1-C_6)-alkoxy” refers to the group –O-(C_1-C_6)-alkyl.

The term “halo-(C_1-C_6)-alkoxy” refers to “C_1-C_6 alkoxy” as defined above, which is substituted with at least one halogen atom. It includes as preferred

embodiments difluoromethoxy and trifluoromethoxy.

The term $5\text{-}HT_{1A}$ receptor "modulator" as used herein includes pure and partial agonists as well as antagonists of the serotonin $5\text{-}HT_{1A}$ receptor. Preferred are "agonists", i.e. compounds with at least partial agonistic activity at the $5\text{-}HT_{1A}$ receptor.

The compounds of the present invention can include enantiomers depending on their asymmetry or diastereoisomers. It is also possible stereoisomerism with regard to double bounds, thereby in some cases the molecule can exist as the (*E*) isomer or the (*Z*) isomer. Each of the different possible enantiomers, diastereoisomers or isomers with regard to double bounds and the mixtures thereof, their racemic and optically pure forms are included in the scope of the present invention.

Optically pure isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques.

The expression stereochemically isomeric forms, as used in this specification, defines all the possible isomeric forms wherein the compounds of formula (I) can be present. Unless otherwise mentioned or indicated, the chemical name of the compounds designates the mixture of all the possible stereochemically isomeric forms, said mixtures containing all the diastereoisomers and enantiomers of the basic molecular structure.

When used hereinafter in this specification, the expression compounds of formula (I) has the object of also including the pharmaceutically acceptable acid addition salts and all the stereoisomeric forms.

The pharmaceutically acceptable acid addition salts previously mentioned in this specification have the object of comprising the acid addition salts that can be conveniently obtained by treatment of the base form of the compounds of formula (I) with appropriate inorganic acids such as hydrochloride or hydrobromic acids, sulphuric, nitric, phosphoric acid and analogous acids; or organic acids, such as, e.g. acetic, hydroxyacetic, propionic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulphonic, ethanesulphonic, benzenesulphonic, *p*-

toluenesulphonic, cyclamic, salicylic, *p*-aminosalicylic, palmoic acids and analogues. Inversely, said forms of acid addition salts can become the free base forms due to treatment with an appropriate base.

The expression acid "addition salt" comprises amorphous as well as crystalline salts and also comprises the hydrates and the forms of solvent addition that the compounds of formula (I) may form. Examples of said forms are hydrates, alcoholates and analogues.

In the field of the present invention physiologically compatible salts will be preferable.

General method of preparation of the compounds of the present invention:

A solution of 1.3 mmol of corresponding halogenated derivative dissolved in 5 mL of dry acetonitrile is added dropwise to 2.0 mmol of the corresponding alkylamine, dissolved in 2 mL of dry acetonitrile. The reaction mixture is heated to 60°C with stirring for 4-6 hours (t.l.c.). After cooling, the solvent is removed at reduced pressure, the residue is dissolved in methylene chloride (25 mL) and is washed with an aqueous solution of 20% potassium carbonate. Then, the organic phase is dried over anhydrous Na_2SO_4 and the solvent is removed at reduced pressure. The resulting oil is purified by silica gel column chromatography in the appropriate solvent mixture, producing the final product as a free base. The compound is transformed to its hydrochloride and is purified by recrystallization.

The final products have been structurally characterized by IR, NMR and quantitative elemental analysis techniques. For greater ease of handling, when the final product is not crystalline, it is transformed in a pharmaceutically acceptable salt, derived from an inorganic or organic acid.

Preferred compounds of the present invention are:

(a) 2-[4-[(Chroman-2(*R*)-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(b) 2-[4-[(Chroman-2-yl)methylamino]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine;

(c) 2-[4-[(Chroman-2-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*a*]pyrazine;

(d) 2-[5-[(Chroman-2-yl)methylamino]pentyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(e) 2-[6-[(Chroman-2-yl)methylamino]hexyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(f) 2-[3-[(Chroman-2-yl)methylamino]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(g) 3-[8-[(Chroman-2-yl)methylamino]octyl]-2,4-dioxothiazolidine;

(h) 2-[4-[(Chroman-2(*S*)-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(i) 2-[8-[(Chroman-2-yl)methylamino]octyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(j) 2-[3-[[(Chroman-2-yl)methylamino]methyl]benzyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

2-[4-[[(Chroman-2-yl)methylamino]methyl]benzyl]-1,3-dioxoperhyd(k)ropyrrolo[1,2-*c*]imidazole;

(l) (*E*)-2-[4-[(Chroman-2-yl)methylamino]but-2-enyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(m) 2-[4-[2-(*o*-Methoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(n) 2-[4-[2-(*m*-Methoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(o) 2-[4-[2-(*o*-Bromophenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(p) 2-[4-[2-(*m*-Bromophenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(q) 2-[4-[2-(*o*-Ethylphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(r) 2-[4-[2-(*m*-Ethylphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(s) 2-[4-[2-(*o*-Isopropylphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(t) 2-[4-[(2-quinolyl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(u) 2-[4-[2-(*o*-Ethoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(v) 2-[4-[2-(*o*-Isopropoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(w) 2-[4-[2-[*m*-(Trifluoromethyl)phenoxy]ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(x) 2-[4-[2-(1,1'-Biphenyl-2-yloxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(y) 2-[4-[2-[*o*-(Acetylamino)phenoxy]ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(z) 2-[4-[2-[*m*-(Acetylamino)phenoxy]ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(aa) 2-[4-[2-[*o*-(Ethoxycarbonyl)phenoxy]ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(bb) 2-[4-[2-(5,6,7,8-tetrahydronaphth-1-yloxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(cc) 2-[4-[2-(2,3-Dimethylphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole;
(dd) 2-[4-[(Chroman-2-yl)methylamino]butyl]-1,4-dioxoperhydropyrido[1,2-*a*]pyrazine;
(ee) (*Z*)-2-[4-[(Chroman-2-yl)methylamino]but-2-enyl]-1,4-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(ff) 3-[4-[2-(o-Ethoxyphenoxy)ethylamino]butyl]-2,4-dioxothiazolidine;
(gg) 3-[6-[2-(*o*-Ethoxyphenoxy)ethylamino]hexyl]-2,4-dioxothiazolidine;
(hh) 3-[8-[2-(*o*-Ethoxyphenoxy)ethylamino]octyl]-2,4-dioxothiazolidine;
(ii) 2-[4-[2-(*o*-Ethoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine;
(jj) 2-[6-[2-(*o*-Ethoxyphenoxy)ethylamino]hexyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine;
(kk) 2-[4-[(2-Quinolyl)methylamino]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine;
(ll) 2-[6-[(2-Quinolyl)methylamino]hexyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine;

their stereochemically isomer forms, hydrates, solvates and pharmaceutically acceptable salts thereof.

The cellular death produced by oxygen and glucose deprivation in primary cultures of rat hippocampal neurons is a model that has a much closer

similarity with cerebral infarction than the cellular death caused by serum deprivation in the culture medium. Whilst in this last model, the death, of an apoptotic nature, takes place due to the elimination of the trophic factors from the medium, oxygen and glucose deprivation causes a death with similar characteristics to that which takes place in an ischemic stroke. In accordance with the predictive value of these in vitro studies, the compound (a) of PCT/ES03/00394 only exercises a protective effect against cerebral infarction induced by permanent occlusion of the middle cerebral artery in rats at a dose of 2 mg/kg. On the other hand, as is indicated further on in the present specification, compound (e) disclosed herein, with a neuroprotective effect equal to (-)-BAYx3702 and about four times greater than the compound (a) of the previous document against death due to anoxia, significantly reduces the volume of cortical infarction in the same focal ischemia model in the rat at a much lower accumulated dose, 0.04 mg/kg, similar to the effective dose of (-)-BAYx3702 in this model.

Taking into account its 5-HT_{1A} receptor affinity and its neuroprotective capacity, the compounds of formula (I) are useful in the treatment and/or prevention of pathological states wherein the 5-HT_{1A} receptor modulators and particularly agonists are indicated, such as, for example, the treatment and/or prophylaxis of cerebral damage caused by thromboembolic stroke or traumatic brain damage, as well as the treatment and/or prevention of Parkinson's disease, depression including particularly endogenous "major" depression, migraine, pain, psychosis such as e.g. schizophrenia; mood disorders, such as anxiety disorders (e.g. obsessional compulsive disorders, generalised anxiety) and aggressive disorders (including mixed aggressive-anxiety/depressive disorders); urinary tract disorders, in particular urinary incontinence, e.g. stress incontinence.

Therefore, according to a second aspect of the present invention, it relates to a pharmaceutical composition that comprises a therapeutically effective quantity of any of the compounds of formula (I) together with a pharmaceutically acceptable carrier.

A third aspect of the present invention relates to the use of compounds of formula (I) in the manufacture of a medicament for the treatment and/or prophylaxis of Parkinson's disease, of the cerebral damage caused by

thromboembolic stroke or traumatic brain damage, depression, migraine, and/or pain, psychosis (e.g. schizophrenia); mood disorders, such as anxiety disorders (e.g. obsessional compulsive disorders, generalised anxiety) and aggressive disorders (including mixed aggressive-anxiety/depressive disorders); urinary tract disorders (e.g. incontinence).

This third aspect may alternatively be formulated as a method for treatment of the diseases mentioned above in a human comprising administering to a human in need thereof an effective amount of pharmaceutical product as described herein.

For ease of administration, the compounds of the present invention can be formulated in various pharmaceutical forms. As appropriate compositions, one can cite all the compositions usually used for drugs administered systemically or locally and externally. To prepare the pharmaceutical compositions of this invention, a therapeutically effective quantity of the particular compound, optionally in the form of an acid addition salt, as an active ingredient, is combined in an intimate mixture with a pharmaceutically acceptable carrier, which can have a large variety of forms, depending on the form of preparation desired to be administered. These pharmaceutical compositions are desirably found in the form of an appropriate unit dose, preferably for oral or rectal administration or by parenteral injection.

For example, in the preparation of the compositions in the form of an oral dose, any of the usual pharmaceutically acceptable carrier can be used, such as, e.g. water buffered and/or isotonic aqueous solutions, glycols, oils, alcohols and analogues in the case of liquid oral preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, ligands, disintegrating agents and analogues, in the case of powders, pills, capsules and tablets.

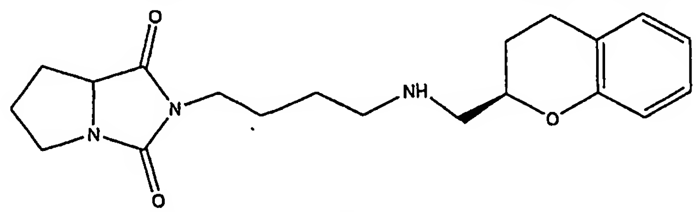
Due to their ease of administration, tablets and capsules represent the most advantageous oral unit dose form, in which case solid pharmaceutical carriers are evidently used. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, although other ingredients can be included, e.g. to favour solubility. Injectable solutions, for example, can be prepared wherein the carrier comprises saline solution, glucose solution or a

mixture of saline solution and glucose solution. Also, if suitable the compounds of the present invention may be also administered transdermally.

The present invention is illustrated with the following non-limiting examples.

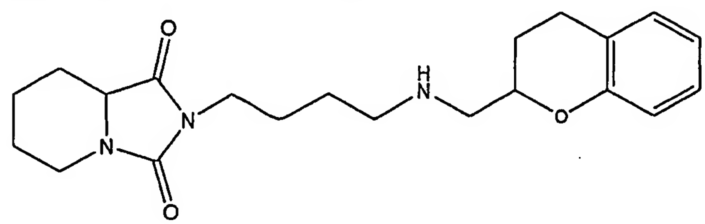
EXAMPLES

Example 1. *2-[4-[(Chroman-2(R)-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (diastereoisomers) (a).



Chromatography: ethyl acetate.
Yield: 35%.
<u>^{1}H-NMR (CDCl$_3$, δ)</u>: 1.47-1.86 (m, 5H, -(CH$_2$)$_2$-, H$_7$), 1.91-2.12 (m, 4H, 2H$_{3'}$, 2H$_6$), 2.16-2.34 (m, 1H, H$_7$), 2.64-2.92 (m, 6H, 2C<u>H$_2$</u>NH, 2H$_{4'}$), 3.16-3.28 (m, 1H, H$_5$), 3.48 (t, *J* = 7.1 Hz, 2H, NCH$_2$), 3.66 (dt, *J* = 11.2, 7.3 Hz, 1H, H$_5$), 4.05 (dd, *J* = 9.1, 7.3 Hz, 1H, H$_{7a}$), 4.11-4.18 (m, 1H, H$_{2'}$), 6.81 (t, *J* = 7.6 Hz, 2H, H$_{6'}$, H$_{8'}$), 7.00-7.10 (m, 2H, H$_{5'}$, H$_{7'}$).
<u>^{13}C-NMR (CDCl$_3$, δ)</u>: 24.6 (C$_3$), 25.6 (C$_4$), 25.8 (CH$_2$), 26.9 (CH$_2$), 27.1 (C$_6$), 27.5 (C$_7$), 38.7 (NCH$_2$), 45.4 (C$_5$), 49.3 (CH$_2$<u>C</u>H$_2$NH), 54.1 (HN<u>C</u>H$_2$CH), 63.2 (C$_{7a}$), 75.0 (C$_2$), 116.7 (C$_{8'}$), 120.1 (C$_{6'}$), 121.9 (C$_{4'a}$), 127.1 (C$_{7'}$), 129.4 (C$_{5'}$), 154.5 (C$_{8'a}$), 160.8 (C$_3$), 173.9 (C$_1$).
<u>Analysis calculated for $C_{20}H_{27}N_3O_3$.HCl</u>:
C, 60.98; H, 7.16; N, 10.67
<u>Found</u>: C, 60.15; H, 7.14; N, 10.45

Example 2. *2-[4-[(Chroman-2-yl)methylamino]butyl]-1,3-dioxoperhydroimidazo[1,5-a]pyridine*, (b).



Chromatography: ethyl acetate.

Yield: 30%.

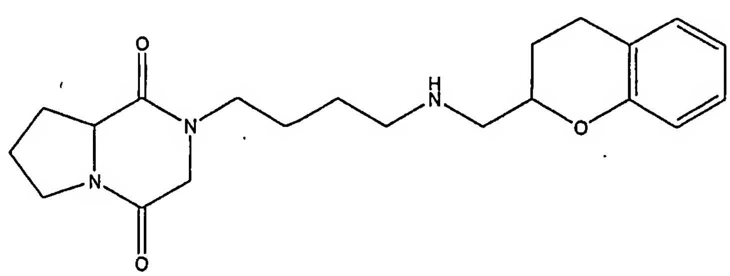
<u>^{1}H-NMR ($CDCl_3$, δ)</u>: 1.06-1.40 (m, 3H, H_{6ax}, H_{7ax}, H_{8ax}), 1.60-1.62 (m, 7H, H_{6ec}, -$(CH_2)_2$-, $2H_{3'}$), 1.88-2.09 (m, 1H, H_{7ec}), 2.11-2.18 (m, 1H, H_{8ec}), 2.71-2.74 (m, 4H, 2NHC<u>H</u>$_2$), 2.85-2.87 (m, 3H, H_{5ax}, $2H_{4'}$), 3.47 (t, 2H, J = 6.6 Hz, NCH_2), 3.67 (dd, 1H, J = 11.9, 4.3 Hz, H_{8a}), 4.03-4.14 (m, 2H, H_{5ec}, $H_{2'}$), 6.76 (t, 2H, J = 7.6 Hz, $H_{6'}$, $H_{8'}$), 6.98 (t, 2H, J = 6.3 Hz, $H_{5'}$, $H_{7'}$).

<u>Analysis calculated for $C_{21}H_{29}N_3O_3.HCl\cdot H_2O$</u>:

C, 59.21; H, 7.57; N, 9.87

<u>Found</u>: C, 58.76; H, 7.01; N, 9.89

Example 3. *2-[4-[(Chroman-2-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-a]pyrazine*, (c).



Chromatography: ethyl acetate.

Yield: 35%.

<u>^{1}H-NMR ($CDCl_3$, δ)</u>: 1.14-2.09 (m, 9H, -$(CH_2)_2$-, $2H_7$, H_8, $2H_{3'}$), 2.28-2.34 (m, 1H, H_8), 2.65-2.93 (m, 6H, 2NHC<u>H</u>$_2$, $2H_{4'}$), 3.29-3.56 (m, 4H, NCH_2, $2H_6$), 3.71 (d, 1H, J = 11.9 Hz, H_3), 4.04-4.14 (m, 3H, H_3, H_{8a}, $H_{2'}$), 6.67-6.80 (m, 2H, $H_{6'}$, $H_{8'}$), 6.95-7.22 (m, 2H, $H_{5'}$, $H_{7'}$).

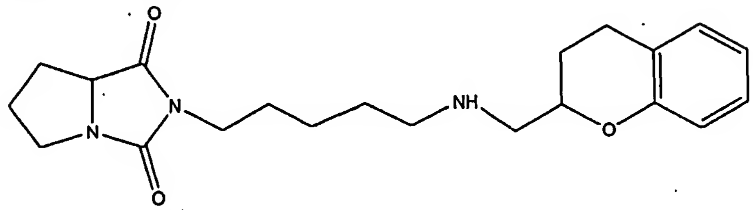
<u>^{13}C-NMR ($CDCl_3$, δ)</u>: 22.8 (C_7), 24.7, 25.0, 25.7, 26.7, 29.0 (-$(CH_2)_2$-, C_8, $C_{3'}$, $C_{4'}$), 45.4 (NCH_2), 46.0 (C_6), 49.4 ($NHCH_2$), 51.9 (C_3), 54.0 ($NHCH_2$), 59.2 (C_{8a}), 74.7 ($C_{2'}$), 116.9 ($C_{8'}$), 120.4 ($C_{6'}$), 122.1 ($C_{4a'}$), 127.4 ($C_{7'}$), 129.7 ($C_{5'}$), 154.6 ($C_{8a'}$), 163.4 (C_4), 167.4 (C_1).

<u>Analysis calculated for $C_{21}H_{29}N_3O_3.HCl\cdot 2H_2O$</u>:

C, 56.81; H, 7.72; N, 9.46

<u>Found</u>: C, 56.73; H, 7.09; N, 9.55

Example 4. *2-[5-[(Chroman-2-yl)methylamino]pentyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (d).



Chromatography: ethyl acetate.

Yield: 32%·

<u>^{1}H-NMR (CDCl$_3$, δ)</u>: 1.34-1.39 (m, 2H, -(CH$_2$)-), 1.61-1.76 (m, 6H, -(CH$_2$)$_2$-, 2H$_{3'}$), 2.01-2.10 (m, 3H, 2H$_6$, H$_7$), 2.17-2.33 (m, 1H, H$_7$), 2.75-2.78 (m, 4H, CH$_2$C<u>H$_2$</u>NH, HNC<u>H$_2$</u>CH), 2.81-2.94 (m, 2H, 2H$_{4'}$), 2.93-2.98 (m, 1H, H$_5$), 3.45 (t, *J* = 7.1 Hz, 2H, NCH$_2$), 3.58-3.78 (m, 1H, H$_5$), 4.06 (dd, *J* = 9.1, 7.3 Hz, 1H, H$_{7a}$), 4.29-4.39 (m, 1H, H$_{2'}$), 6.82-6.89 (m, 2H, H$_{6'}$, H$_{8'}$), 7.02-7.11 (m, 2H, H$_{5'}$, H$_{7'}$).

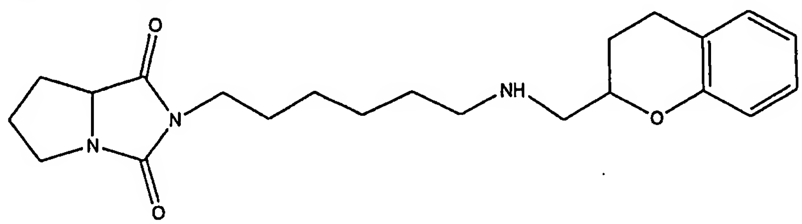
<u>^{13}C-NMR (CDCl$_3$, δ)</u>: 23.6 (CH$_2$), 24.9 (C$_{3'}$), 25.1 (C$_{4'}$), 26.9 ((CH$_2$)$_2$), 27.2 (C$_6$), 27.4 (C$_7$), 38.0 (NCH$_2$), 38.5 (C$_5$), 45.3 (CH$_2$<u>C</u>H$_2$NH), 47.9 (HN<u>C</u>H$_2$CH), 63.3 (C$_{7a}$), 70.9 (C$_2$), 117.1 (C$_{8'}$), 121.0 (C$_{6'}$), 121.2 (C$_{4'a}$), 127.4 (C$_{5'}$), 129.3 (C$_{7'}$), 153.0 (C$_{8'a}$), 160.7 (C$_3$), 173.9 (C$_1$).

<u>Analysis calculated for $C_{21}H_{29}N_3O_3$.HCl.H_2O</u>:

C, 59.21; H, 7.57; N, 9.87

<u>Found</u>: C, 59.19; H, 7.17; N, 9.64

Example 5. *2-[6-[(Chroman-2-yl)methylamino]hexyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (e).



Chromatography: chloroform/methanol, 9.5:0.5.

Yield: 35%·

<u>^{1}H-NMR (CDCl$_3$, δ)</u>: 1.28-1.35 (m, 4H, -(CH$_2$)$_2$-), 1.60-1.80 (m, 6H, -(CH$_2$)$_2$-, 2H$_{3'}$), 1.96-2.14 (m, 3H, 2H$_6$, H$_7$), 2.17-2.33 (m, 1H, H$_7$), 2.77-3.03 (m, 6H, CH$_2$C<u>H$_2$</u>NH, HNC<u>H$_2$</u>CH, 2H$_{4'}$), 3.17-3.30 (m, 1H, H$_5$), 3.45 (t, *J* = 7.1 Hz, 2H, NCH$_2$), 3.58-3.78 (m, 1H, H$_5$), 4.06 (dd, *J* = 9.1, 7.3 Hz, 1H, H$_{7a}$), 4.29-4.39 (m, 1H, H$_{2'}$), 6.80-6.93 (m, 2H, H$_{6'}$, H$_{8'}$), 7.00-7.08 (m, 2H, H$_{5'}$, H$_{7'}$).

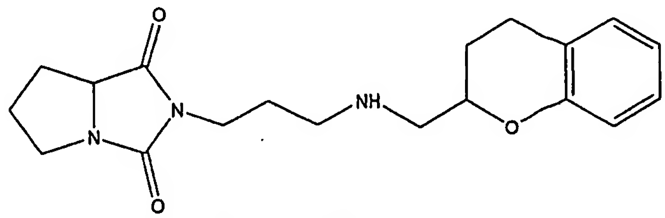
<u>^{13}C-NMR (CDCl$_3$, δ)</u>: 24.1 (CH$_2$), 24.3 (C$_{3'}$), 25.5 (C$_{4'}$), 26.3, 26.5, 27.0 ((CH$_2$)$_3$), 27.5 (C$_6$), 27.8 (C$_7$), 38.7 (NCH$_2$), 45.5 (C$_5$), 49.2 (CH$_2$<u>C</u>H$_2$NH), 53.1 (HN<u>C</u>H$_2$CH), 63.3 (C$_{7a}$), 72.7 (C$_{2'}$), 116.9 (C$_{8'}$), 120.4 (C$_{6'}$), 121.7 (C$_{4'a}$), 127.3 (C$_{5'}$), 129.5 (C$_{7'}$), 154.1 (C$_{8'a}$), 160.9 (C$_3$), 174.0 (C$_1$).

<u>Analysis calculated for $C_{22}H_{31}N_3O_3$.HCl.H_2O</u>:

C, 60.06; H, 7.79; N, 9.55

<u>Found</u>: C, 60.46; H, 7.41; N, 9.54

Example 6. *2-[3-[(Chroman-2-yl)methylamino]propyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (f).



Chromatography: ethyl acetate.

Yield: 40%.

<u>^{1}H-NMR (CDCl$_3$, δ)</u>: 1.64-2.32 (m, 8H, -(CH$_2$)-, 2H$_6$, 2H$_7$, 2H$_{3'}$), 2.68-2.88 (m, 6H, 2C<u>H$_2$</u>NH, 2H$_{4'}$), 3.18-3.30 (m, 1H, H$_5$), 3.58 (t, 2H, J = 6.8 Hz, NCH$_2$), 3.65-3.70 (m, 1H, H$_5$), 4.03-4.17 (m, 2H, H$_{7a}$, H$_{2'}$), 6.79-6.86 (m, 2H, H$_{6'}$, H$_{8'}$), 7.02-7.11 (m, 2H, H$_{5'}$, H$_{7'}$).

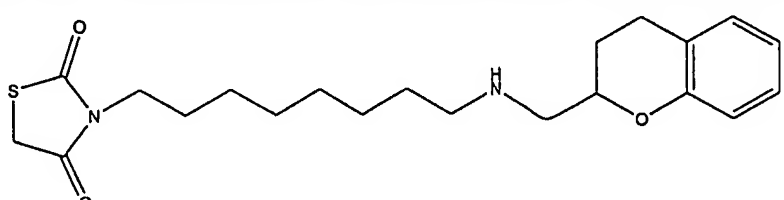
<u>^{13}C-NMR (CDCl$_3$, δ)</u>: 24.6 (C$_{3'}$), 25.6 (C$_{4'}$), 26.9 (CH$_2$), 27.5 (C$_6$), 28.1 (C$_7$), 36.9 (NCH$_2$), 45.5 (C$_5$), 46.9 (CH$_2$<u>C</u>H$_2$NH), 54.0 (HN<u>C</u>H$_2$CH), 63.3 (C$_{7a}$), 74.9 (C$_2$), 116.8 (C$_{8'}$), 120.2 (C$_{6'}$), 122.0 (C$_{4'a}$), 127.2 (C$_{7'}$), 129.5 (C$_{5'}$), 154.6 (C$_{8'a}$), 160.9 (C$_3$), 174.0 (C$_1$).

<u>Analysis calculated for $C_{19}H_{25}N_3O_3 \cdot HCl$</u>:

C, 60.07; H, 6.90; N, 11.06

<u>Found</u>: C, 59.65; H, 6.91; N, 10.55

Example 7. *3-[8-[(Chroman-2-yl)methylamino]octyl]-2,4-dioxothiazolidine*, (g).



Chromatography: ethyl acetate.

Yield: 35%; m.p. 108-111 °C.

^{1}H-NMR (CDCl$_3$, δ): 1.29-1.31 (m, 8H, -$(CH_2)_4$-), 1.55-1.66 (m, 4H, CH_2, 2H$_{3'}$), 1.71-1.86 (m, 2H, CH_2), 2.70-2.93 (m, 6H, 2NHC$\underline{H_2}$, 2H$_{4'}$), 3.60 (t, J = 7.6 Hz, 2H, NCH_2), 3.94 (s, 2H, 2H$_5$), 4.19-4.25 (m, 2H, H$_{2'}$, NH), 6.80-6.86 (m, 2H, H$_{6'}$, H$_{8'}$), 7.01-7.11 (m, 2H, H$_{5'}$, H$_{7'}$).

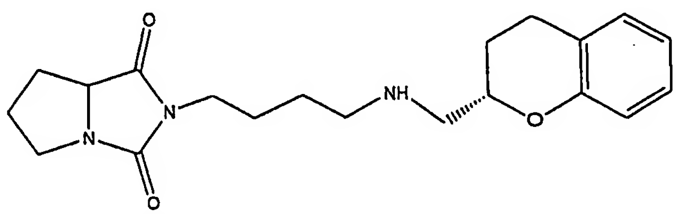
^{13}C-NMR (CDCl$_3$, δ): 24.3, 25.4, 26.4, 26.9, 27.3, 28.8, 28.9, 29.0 (-$(CH_2)_6$-, C$_{3'}$, C$_{4'}$), 33.5 (C$_5$), 41.9 (NCH_2), 49.3, 53.3 (2CH_2NH), 74.0 (C$_{2'}$), 116.6 (C$_{8'}$), 120.2 (C$_{6'}$), 121.7 (C$_{4a'}$), 127.1 (C$_{7'}$), 129.3 (C$_{5'}$), 154.2 (C$_{8a'}$), 171.3, 171.7 (C$_2$, C$_4$).

Analysis calculated for $C_{21}H_{30}N_2O_3S.HCl\cdot3H_2O$:

C, 52.43; H, 7.75; N, 5.82

Found: C, 52.33; H, 6.78; N, 5.79

Example 8. *2-[4-[(Chroman-2(S)-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (diastereoisomers) (h).



Chromatography: ethyl acetate.

Yield: 38%.

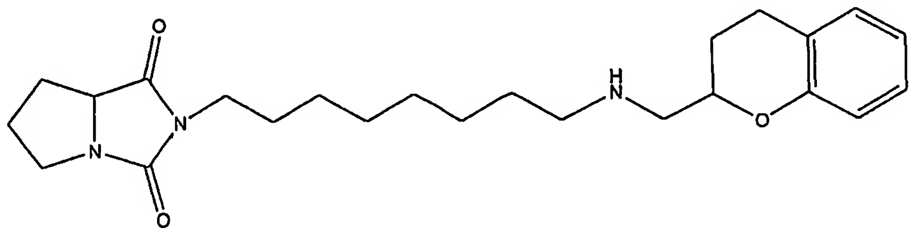
$[\alpha]^{25}_D$ = +65 (c = 0.5, $CHCl_3$).

Analysis calculated for $C_{21}H_{30}N_2O_3S.HCl\cdot3H_2O$:

C, 53.62; H, 7.65; N, 9.38

Found: C, 53.45; H, 7.34; N, 9.45

Example 9. *2-[8-[(Chroman-2-yl)methylamino]octyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (i).



Chromatography: ethyl acetate.

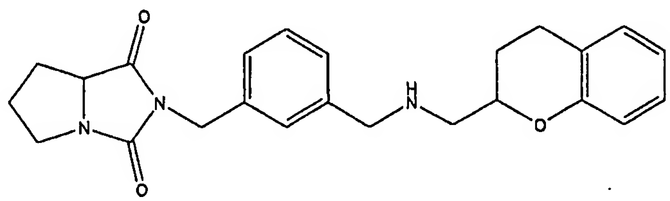
Yield: 35%.

^{1}H-RMN (CDCl$_3$, δ): 1.29-1.31 (m, 8H, -$(CH_2)_4$-), 1.55-1.88 (m, 7H, -$(CH_2)_2$-, 2H$_{3'}$, H$_7$), 1.94-2.34 (m, 3H, 2H$_6$, H$_7$), 2.54 (br s, 1H, NH), 2.66-2.97 (m, 6H,

$2C\underline{H}_2NH$, $2H_{4'}$), 3.18-3.29 (m, 1H, H_5), 3.44 (t, 2H, J = 7.3 Hz, NCH_2), 3.62-3.74 (m, 1H, H_5), 4.06 (dd, 1H, J = 7.8, 7.6 Hz, H_{7a}); 4.14-4.21 (m, 1H, $H_{2'}$), 6.80-6.86 (m, 2H, $H_{6'}$, $H_{8'}$), 7.01-7.11 (m, 2H, $H_{5'}$, $H_{7'}$).

<u>^{13}C-RMN ($CDCl_3$, δ)</u>: 24.6, 25.7, 26.6, 27.0, 27.1, 27.6, 27.9, 29.0 (-$(CH_2)_6$-, $C_{3'}$, $C_{4'}$), 29.3 (C_6), 29.6 (C_7), 39.0 (NCH_2), 45.5 (C_5), 49.8 ($CH_2\underline{C}H_2NH$), 54.0 ($HN\underline{C}H_2CH$), 63.3 (C_{7a}), 74.7 ($C_{2'}$), 116.8 ($C_{8'}$), 121.2 ($C_{6'}$), 121.9 ($C_{4'a}$), 127.2 ($C_{5'}$), 129.5 ($C_{7'}$), 154.5 ($C_{8'a}$), 160.9 (C_3), 174.0 (C_1).

Example 10. *2-[3-[[(Chroman-2-yl)methylamino]methyl]benzyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (j).



Chromatography: ethyl acetate.

Yield: 40%.

<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.58-2.26 (m, 6H, $2H_6$, $2H_7$, $2H_{3'}$), 2.69-2.96 (m, 4H, $C\underline{H}_2NH$, $2H_{4'}$), 3.23 (ddd, 1H, J = 12.5, 7.6, 5.4 Hz, H_5), 3.69 (dt, 1H, J = 11.2, 7.6 Hz, H_5), 3.85 (s, 2H, CH_2Ar), 4.04-4.22 (m, 2H, H_{7a}, $H_{2'}$), 4.62 (s, 2H, NCH_2), 6.82 (t, 2H, J = 6.8 Hz, $H_{6'}$, $H_{8'}$), 7.02-7.11 (m, 2H, $H_{5'}$, $H_{7'}$), 7.26-7.34 (m, 4H, ArH).

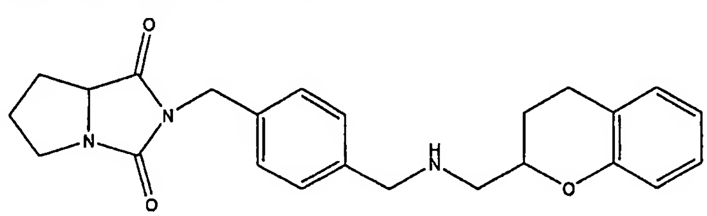
<u>^{13}C-RMN ($CDCl_3$, δ)</u>: 24.7 ($C_{3'}$), 25.6 ($C_{4'}$), 27.0 (C_6), 27.5 (C_7), 42.5 (NCH_2), 45.5 (C_5), 53.5, 53.6 ($2CH_2NH$), 63.4 (C_{7a}), 75.2 (C_2), 116.8 ($C_{8'}$), 120.2 ($C_{6'}$), 122.0 ($C_{4'a}$), 127.0, 127.2, 127.7, 128.2, 128.8 ($C_{7'}$, phenyl), 129.5 ($C_{5'}$), 136.1, 140.7 (phenyl), 154.7 ($C_{8'a}$), 160.5 (C_3), 173.6 (C_1).

<u>Analysis calculated for $C_{24}H_{27}N_3O_3.HCl{\cdot}3H_2O$:</u>

C, 58.12; H, 6.91; N, 8.47

<u>Found</u>: C, 58.19; H, 6.51; N, 8.07

Example 11. *2-[4-[[(Chroman-2-yl)methylamino]methyl]benzyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (k).



Chromatography: ethyl acetate.

Yield: 44%.

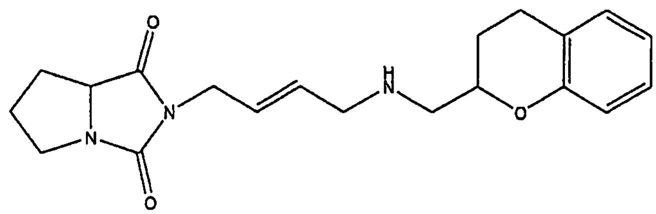
^{1}H-RMN (CDCl$_3$, δ): 1.57-2.29 (m, 6H, 2H$_6$, 2H$_7$, 2H$_{3'}$), 2.75-2.95 (m, 4H, C$\underline{H}_2$NH, 2H$_{4'}$), 3.24 (ddd, 1H, J = 12.4, 7.3, 5.4 Hz, H$_5$), 3.69 (dt, 1H, J = 11.2, 7.6 Hz, H$_5$), 3.84 (s, 2H, CH$_2$Ar), 4.04-4.22 (m, 2H, H$_{7a}$, H$_{2'}$), 4.61 (s, 2H, NCH$_2$), 6.82 (t, 2H, J = 8.1 Hz, H$_{6'}$, H$_{8'}$), 7.01-7.11 (m, 2H, H$_{5'}$, H$_{7'}$), 7.28-7.38 (m, 4H, ArH).

Analysis calculated for $C_{24}H_{27}N_3O_3 \cdot HCl \cdot 2H_2O$:

C, 60.31; H, 6.75; N, 8.79

Found: C, 60.71; H, 6.40; N, 8.52

Example 12. *(E)-2-[4-[(Chroman-2-yl)methylamino]but-2-enyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (I).



Chromatography: ethyl acetate.

Yield: 43%.

^{1}H-RMN (CDCl$_3$, δ): 1.63-2.31 (m, 6H, 2H$_6$, 2H$_7$, 2H$_{3'}$), 2.65-2.93 (m, 4H, C$\underline{H}_2$NH, 2H$_{4'}$), 3.17-3.31 (m, 3H, C$\underline{H}_2$NH, H$_5$), 3.67 (dt, 1H, J = 11.2, 7.6 Hz, H$_5$), 4.03-4.14 (m, 4H, NCH$_2$, H$_{7a}$, H$_{2'}$), 5.54-5.85 (m, 2H, CH=CH), 6.77-6.85 (m, 2H, H$_{6'}$, H$_{8'}$), 7.00-7.10 (m, 2H, H$_{5'}$, H$_{7'}$).

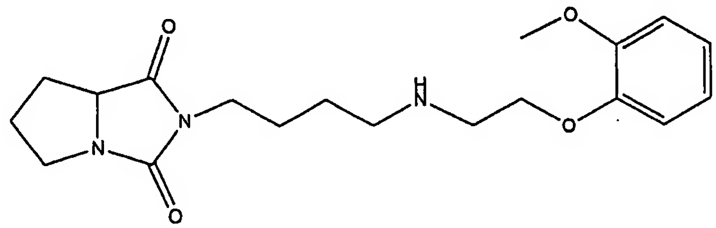
^{13}C-RMN (CDCl$_3$, δ): 24.7 (C$_{3'}$), 25.7 (C$_{4'}$), 27.1 (C$_6$), 27.6 (C$_7$), 40.2 (NCH$_2$), 45.6 (C$_5$), 50.9, 53.6 (2CH$_2$NH), 63.5 (C$_{7a}$), 75.1 (C$_2$), 116.8 (C$_{8'}$), 120.3 (C$_{6'}$), 122.1 (C$_{4'a}$), 124.8 (CH), 127.3 (C$_{7'}$), 129.6 (C$_{5'}$), 132.3 (CH), 154.6 (C$_{8'a}$), 160.4 (C$_3$), 173.6 (C$_1$).

Analysis calculated for $C_{20}H_{25}N_3O_3 \cdot HCl \cdot 4H_2O$:

C, 51.78; H, 7.39; N, 9.06

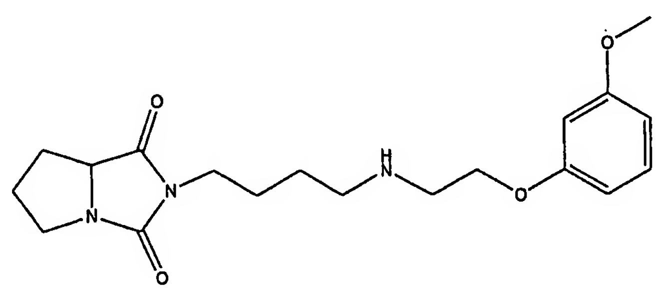
Found: C, 52.16; H, 7.00; N, 9.16

Example 13. *2-[4-[2-(o-Methoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole* (m).



Chromatography: ethyl acetate.
Yield: 38%.
<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.63-1.71 (m, 5H, $-(CH_2)_2-$, H_7), 1.99-2.29 (m, 3H, $2H_6$, H_7), 2.78 (t, 2H, J = 6.8 Hz, C<u>H</u>$_2$NH), 3.01-3.10 (m, 2H, C<u>H</u>$_2$NH), 3.21 (ddd, 1H, J = 11.2, 6.1, 5.6 Hz, H_5), 3.57-3.80 (m, 3H, NCH_2, H_5), 3.83 (s, 3H, OCH_3), 4.00-4.18 (m, 3H, OCH_2, H_{7a}), 6.87-6.90 (m, 4H, ArH).
<u>^{13}C-RMN ($CDCl_3$, δ)</u>: 25.5, 25.6 ($-(CH_2)_2-$), 26.5, 27.4 (C_6, C_7), 38.4 (NCH_2), 45.4 (C_5), 48.1, 48.6 ($2CH_2NH$), 63.2 (C_{7a}), 67.7 (OCH_3), 71.0 (OCH_2), 111.8 ($C_{6'}$), 120.9 ($C_{4'}$), 125.9, 129.7 ($C_{3'}$, $C_{5'}$), 130.5 ($C_{2'}$), 147.8 ($C_{1'}$), 160.6 (C_3), 173.9 (C_1).
<u>Analysis calculated for $C_{19}H_{27}N_3O_4.HCl.4H_2O$</u>:
C, 48.56; H, 7.72; N, 8.94
<u>Found</u>: C, 48.16; H, 7.32; N, 8.48

Example 14. *2-[4-[2-(m-Methoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (n).



Chromatography: ethyl acetate.
Yield: 38%.
<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.42-1.70 (m, 4H, $-(CH_2)_2-$), 1.95-2.06 (m, 3H, $2H_6$, H_7), 2.10-2.19 (m, 1H, H_7), 2.64 (t, 2H, J = 6.8 Hz, C<u>H</u>$_2$NH), 2.92 (t, 2H, J = 5.4 Hz, C<u>H</u>$_2$NH), 3.16 (ddd, 1H, J = 11.2, 7.3, 5.4 Hz, H_5), 3.39 (t, 2H, J = 6.3 Hz,

NCH_2), 3.59 (dt, 1H, J = 11.3, 7.6 Hz, H_5), 3.71 (s, 3H, OCH_3), 3.97-4.07 (m, 3H, OCH_2, H_{7a}), 6.41-6.47 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$), 7.10 (t, 1H, J = 7.8 Hz, $H_{5'}$).

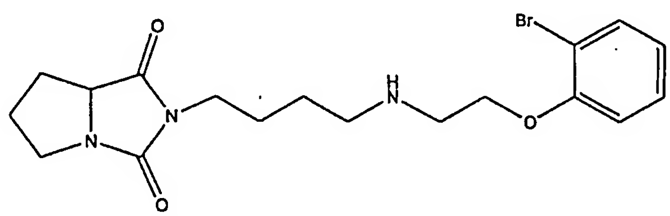
^{13}C-RMN ($CDCl_3$, δ): 25.8 (-$(CH_2)_2$-), 27.0, 27.5 (C_6, C_7), 38.7 (NCH_2), 45.6 (C_5), 48.3, 49.0 ($2CH_2NH$), 63.2 (C_{7a}), 67.2, 68.6 (OCH_3, OCH_2), 101.0 ($C_{2'}$), 106.4, 106.6 ($C_{4'}$, $C_{6'}$), 129.8 ($C_{5'}$), 138.9 ($C_{1'}$), 160.0 ($C_{3'}$), 160.8 ($C_{3'}$), 173,9 (C_1).

Analysis calculated for $C_{19}H_{27}N_3O_4.HCl.3H_2O$:

C, 50.49; H, 7.58; N, 9.30

Found: C, 50.71; H, 7.18; N, 8.90

Example 15. *2-[4-[2-(o-Bromophenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (o).



Chromatography: ethyl acetate.

Yield: 48%; m.p. 98-99 ºC.

^{1}H-RMN ($CDCl_3$, δ): 1.46-1.69 (m, 4H, -$(CH_2)_2$-), 1.98-2.20 (m, 4H, $2H_6$, $2H_7$), 2.70 (t, 2H, J = 6.8 Hz, $C\underline{H_2}NH$), 3.00 (t, 2H, J = 5.1 Hz, $C\underline{H_2}NH$), 3.19 (ddd, 1H, J = 11.2, 7.3, 5.4 Hz, H_5), 3.46 (t, 2H, J = 7.1 Hz, NCH_2), 3.64 (dt, 1H, J = 11.2, 7.6 Hz, H_5), 3.99-4.12 (m, 3H, OCH_2, H_{7a}), 6.80 (dt, 2H, J = 8.1, 8.0 Hz, $H_{4'}$, $H_{6'}$), 7.21 (td, 1H, J = 5.9, 1.2 Hz, $H_{5'}$), 7.49 (dd, 1H, J = 7.8, 1.4 Hz, $H_{3'}$).

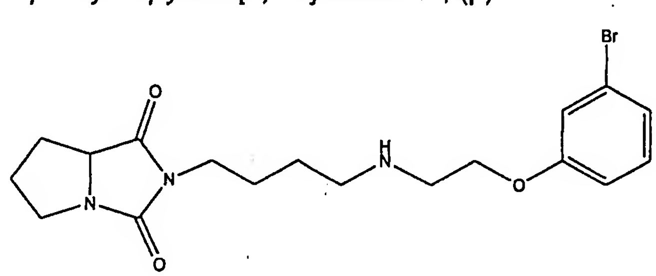
^{13}C-RMN ($CDCl_3$, δ): 25.6, 26.8 (-$(CH_2)_2$-), 26.9, 27.4 (C_6, C_7), 38.6 (NCH_2), 45.4 (C_5), 48.2, 48.9 ($2CH_2NH$), 63.1 (C_{7a}), 68.4 (OCH_2), 112.2 ($C_{2'}$), 113.4 ($C_{6'}$), 121.9 ($C_{4'}$), 128.3 ($C_{5'}$), 133.1 ($C_{3'}$), 155.0 ($C_{1'}$), 160.6 (C_3), 173.8 (C_1).

Analysis calculated for $C_{18}H_{24}BrN_3O_3.HCl.2H_2O$:

C, 44.78; H, 6.05; N, 8.70

Found: C, 44.38; H, 5.65; N, 9.05

Example 16. *2-[4-[2-(m-Bromophenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (p).



Chromatography: ethyl acetate.

Yield: 42%; m.p. 140-143 °C.

^{1}H-RMN ($CDCl_3$, δ): 1.42-1.74 (m, 4H, -$(CH_2)_2$-), 1.94-2.22 (m, 4H, $2H_6$, $2H_7$), 2.68 (t, 2H, J = 7.1 Hz, C<u>H</u>$_2$NH), 2.96 (t, 2H, J = 5.1 Hz, C<u>H</u>$_2$NH), 3.19 (ddd, 1H, J = 11.2, 7.3, 5.1 Hz, H_5), 3.45 (t, 2H, J = 7.8 Hz, NCH_2), 3.64 (dt, 1H, J = 11.2, 7.6 Hz, H_5), 3.99-4.14 (m, 3H, OCH_2, H_{7a}), 6.78-6.83 (m, 1H, $H_{4'}$), 7.02-7.10 (m, 3H, $H_{2'}$, $H_{5'}$, $H_{6'}$).

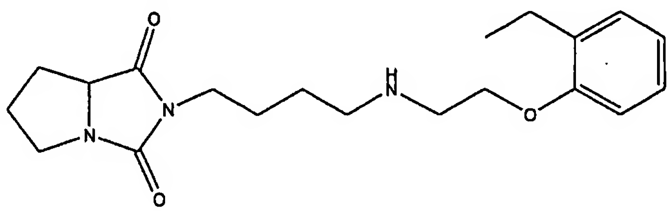
^{13}C-RMN ($CDCl_3$, δ): 25.6, 26.9, 27.4 (-$(CH_2)_2$-, C_6, C_7), 38.6 (NCH_2), 45.4 (C_5), 48.4, 49,0 ($2CH_2NH$), 63.2 (C_{7a}), 67.3 (OCH_2), 113.4 ($C_{6'}$), 117.7 ($C_{2'}$), 122.6 ($C_{3'}$), 123.8 ($C_{4'}$), 130.4 ($C_{5'}$), 159.5 ($C_{1'}$), 160.7 (C_3), 173.8 (C_1).

Analysis calculated for $C_{18}H_{24}BrN_3O_3.HCl.2H_2O$:

C, 44.78; H, 6.05; N, 8.70

Found: C, 44.47; H, 5.65; N, 9.30

Example 17. *2-[4-[2-(o-Ethylphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (q).



Chromatography: chloroform/methanol, 9.5:0.5.

Yield: 28%; m.p. 115-118 °C (hexane).

^{1}H-RMN ($CDCl_3$, δ): 1.19 (t, 3H, J = 7.4 Hz, CH_3), 1.59-1.74 (m, 5H, -$(CH_2)_2$-, H_7), 1.97-2.09 (m, 2H, $2H_6$), 2.17-2.28 (m, 1H, H_7), 2.63 (q, 2H, J = 7.6 Hz, C<u>H</u>$_2$CH$_3$), 2.80 (t, 2H, J = 7.1 Hz, C<u>H</u>$_2$NH), 3.08 (t, 2H, J = 5.1 Hz, C<u>H</u>$_2$NH), 3.17-3.29 (m, 1H, H_5), 3.50 (t, 2H, J = 6.8 Hz, NCH_2), 3.61-3.75 (m, 1H, H_5), 4.02-4.15 (m, 3H, OCH_2, H_{7a}), 6.82-6.94 (m, 2H, $H_{4'}$, $H_{6'}$), 7.11-7.17 (m, 2H, $H_{3'}$, $H_{5'}$).

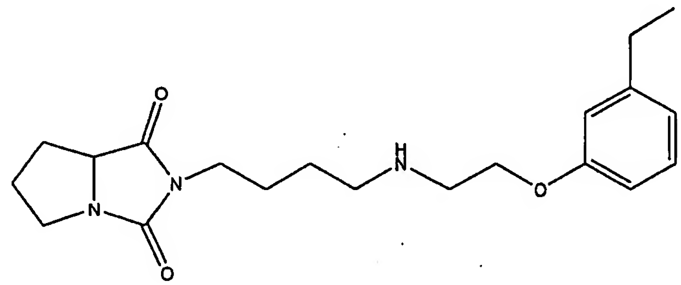
^{13}C-RMN ($CDCl_3$, δ): 12.2 (CH_3), 23.2, 25.7, 26.6 (<u>C</u>H$_2$CH$_3$, -$(CH_2)_2$-), 27.0, 27.5 (C_6, C_7), 38.6 (<u>C</u>H$_2$NCO), 45.5 (C_5), 48.5, 48.9 ($2CH_2NH$), 63.3 (OCH_2, C_{7a}), 111.3 ($C_{6'}$), 120.8 ($C_{4'}$), 126.8, 129.0 ($C_{3'}$, $C_{5'}$), 132.7 ($C_{2'}$), 156.3 ($C_{1'}$), 160.8 (C_3), 167.4 (C_1).

Analysis calculated for $C_{20}H_{29}N_3O_3.HCl.2H_2O$:

C, 55.61; H, 7.93; N, 9.73

Found: C, 55.89; H, 7.53; N, 9.81

Example 18. *2-[4-[2-(m-Ethylphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (r).



Chromatography: ethyl acetate.

Yield: 43%.

<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.24 (t, 3H, J = 7.6 Hz, CH_3), 1.59-1.74 (m, 5H, -$(CH_2)_2$-, H_7), 1.97-2.09 (m, 2H, $2H_6$), 2.17-2.28 (m, 1H, H_7), 2.63-2.74 (m, 4H, $C\underline{H}_2CH_3$, $C\underline{H}_2NH$), 3.12 (t, 2H, J = 5.1 Hz, $C\underline{H}_2NH$), 3.17-3.29 (m, 1H, H_5), 3.50 (t, 2H, J = 7.1 Hz, NCH_2), 3.61-3.75 (m, 1H, H_5), 4.02-4.15 (m, 3H, OCH_2, H_{7a}), 6.72-6.86 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$), 7.21 (t, 1H, J = 7.8 Hz, $H_{5'}$).

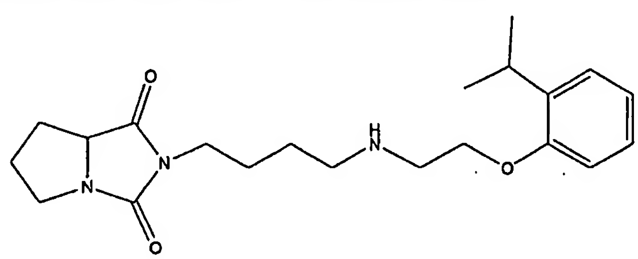
<u>^{13}C-RMN ($CDCl_3$, δ)</u>: 15.5 (CH_3), 25.5, 25.8, 27.0 ($\underline{C}H_2CH_3$, -$(CH_2)_2$-), 27.3, 27.6 (C_6, C_7), 38.8 (NCH_2), 45.6 (C_5), 48.7, 49.0 ($2CH_2NH$), 63.4 (C_{7a}), 66.9 (OCH_2), 111.5 ($C_{2'}$), 114.4 ($C_{6'}$), 120.6 ($C_{4'}$), 129.3 ($C_{5'}$), 146.0 ($C_{3'}$), 158.9 ($C_{1'}$), 160.9 (C_3), 174.0 (C_1).

<u>Analysis calculated for $C_{20}H_{29}N_3O_3.HCl.H_2O$:</u>

C, 58.03; H, 7.79; N, 10.15

<u>Found</u>: C, 57.92; H, 7.91; N, 10.12

Example 19. *2-[4-[2-(o-Isopropylphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (s).



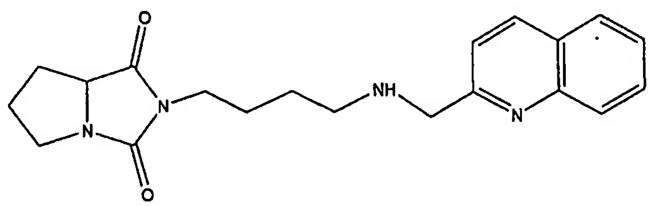
Chromatography: ethyl acetate.

Yield: 23%.

<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.21 (d, 6H, J = 7.9 Hz, $2CH_3$), 1.44-1.76 (m, 5H, -$(CH_2)_2$-, H_7), 1.95-2.32 (m, 3H, $2H_6$, H_7), 2.71 (t, 2H, J = 6.8 Hz, $C\underline{H}_2NH$), 3.02 (t, 2H, J = 5.1 Hz, $C\underline{H}_2NH$), 3.17-3.37 (m, 2H, CH, H_5), 3.49 (t, 2H, J = 7.1 Hz, NCH_2), 3.67

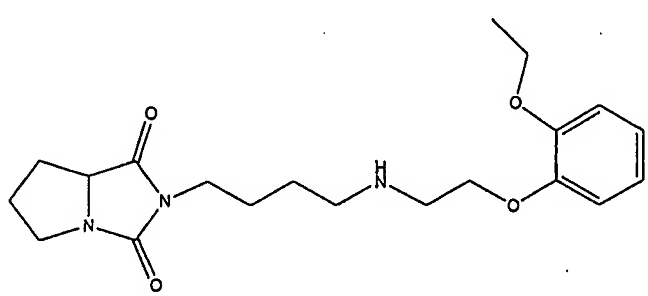
(dt, 1H, J = 7.6, 3.9 Hz, H_5), 4.00-4.09 (m, 3H, OCH_2, H_{7a}), 6.82-6.96 (m, 2H, $H_{4'}$, $H_{6'}$), 7.09-7.22 (m, 2H, $H_{3'}$, $H_{5'}$).
^{13}C-RMN ($CDCl_3$, δ): 22.7 (CH_3), 25.9, 26.9, 27.0, 27.3, 27.6 ($-(CH_2)_2-$, CH, C_6, C_7), 38.8 (NCH_2), 45.6 (C_5), 49.0, 49.2 ($2CH_2NH$), 63.4 (C_{7a}), 67.5 (OCH_2), 111.5 ($C_{6'}$), 120.8 ($C_{4'}$), 126.1, 126.6 ($C_{3'}$, $C_{5'}$), 135.3 ($C_{2'}$), 157.5 ($C_{1'}$), 160.8 (C_3), 173.9 (C_1).

Example 20. *2-[4-[(2-Quinolyl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (t).



Chromatography: ethyl acetate.
Yield: 33%; m.p. 125-126 ºC
IR ($CHCl_3$, cm^{-1}): 1770, 1708 (CONCON), 1601, 1504, 1442, 1416 (Ar).
^{1}H-RMN ($CDCl_3$, δ): 1.52-1.67 (m, 5H, $-(CH_2)_2-$, H_7), 1.90-2.27 (m, 3H, $2H_6$, H_7), 2.50 (t, 2H, J = 6.3 Hz, CH_2NH), 3.01-3.24 (m, 1H, H_5), 3.42 (t, 2H, J = 6.8 Hz, NCH_2), 3.53-3.69 (m, 1H, H_5), 3.91-4.00 (m, 3H, CH_2Ar, H_{7a}), 7.47 (t, J = 7.1 Hz, 1H, $H_{6'}$), 7.62-7.77 (m, 3H, $H_{3'}$, $H_{5'}$, $H_{7'}$), 8.02 (d, J = 8.3 Hz, 1H, $H_{4'}$), 8.11 (d, J = 8.5 Hz, 1H, $H_{8'}$).
^{13}C-RMN ($CDCl_3$, δ): 24.4, 25.8, 26.8, 27.4 ($2CH_2$, C_6, C_7), 38.7 (NCH_2), 45.4 (C_5), 53.8, 54.1 (CH_2Ar, CH_2NH), 63.1 (C_{7a}), 120.9 ($C_{3'}$), 126.0 ($C_{6'}$), 127.2, 127.4 ($C_{5'}$, $C_{8'}$), 128.9, 129.2 ($C_{4'}$, $C_{7'}$), 130.7 ($C_{4'a}$), 155.9 ($C_{2'}$), 160.5 ($C_{8'a}$), 160.7 (C_3), 173.8 (C_1).

Example 21. *2-[4-[2-(o-Ethoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (u).



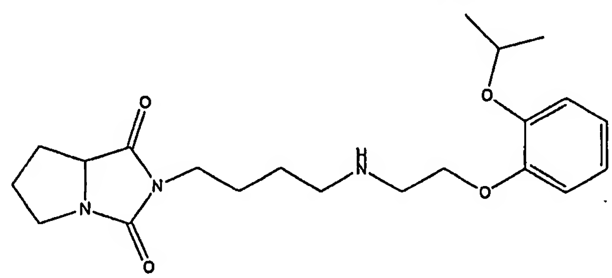
Chromatography: ethyl acetate.

Yield: 30%.

^{1}H-RMN ($CDCl_3$, δ): 1.43 (t, 3H, J = 6.8 Hz, CH_3), 1.62-1.72 (m, 5H, -$(CH_2)_2$-, H_7), 1.94-2.27 (m, 3H, $2H_6$, H_7), 2.78 (t, 2H, J = 6.6 Hz, C$\underline{H_2}$NH), 3.06 (t, 2H, J = 5.1 Hz, C$\underline{H_2}$NH), 3.22 (ddd, 1H, J = 12.4, 7.3, 5.1 Hz, H_5), 3.44-3.72 (m, 3H, NCH_2, H_5), 4.01-4.17 (m, 4H, OCH_2, H_{7a}, C$\underline{H_2}$$CH_3$), 6.87-6.92 (m, 4H, ArH).

^{13}C-RMN ($CDCl_3$, δ): 14.8 (CH_3), 25.6, 26.4, 26.8, 27.4 (-$(CH_2)_2$-, C_6, C_7), 38.5 (NCH_2), 45.4 (C_5), 48.3, 48.7 ($2CH_2NH$), 63.2 (C_{7a}), 64.3 ($\underline{C}H_2CH_3$), 68.3 (OCH_2), 113.6, 115.1, 120.9, 121.8 ($C_{6'}$, $C_{4'}$, $C_{3'}$, $C_{5'}$), 148.3 ($C_{2'}$), 149.1 ($C_{1'}$), 160.7 (C_3), 173.8 (C_1).

Example 22. *2-[4-[2-(o-Isopropoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole*, (v).



Chromatography: ethyl acetate.

Yield: 23%.

^{1}H-RMN ($CDCl_3$, δ): 1.33 (d, 6H, J = 6.1 Hz, $2CH_3$), 1.55-1.71 (m, 4H, -$(CH_2)_2$-), 2.04-2.26 (m, 4H, $2H_6$, $2H_7$), 2.72 (q, 2H, J = 6.2 Hz, C$\underline{H_2}$NH), 3.02 (q, 2H, J = 5.1 Hz, C$\underline{H_2}$NH), 3.23 (ddd, 1H, J = 12.5, 7.3, 5.1 Hz, H_5), 3.48 (t, 2H, J = 6.8 Hz, NCH_2), 3,67 (dt, 1H, J = 11.0, 7.8 Hz, H_5), 4.02-4.13 (m, 3H, OCH_2, H_{7a}), 4.45 (sept, 1H, J = 6.1 Hz, CH), 6.89-6.92 (m, 4H, ArH).

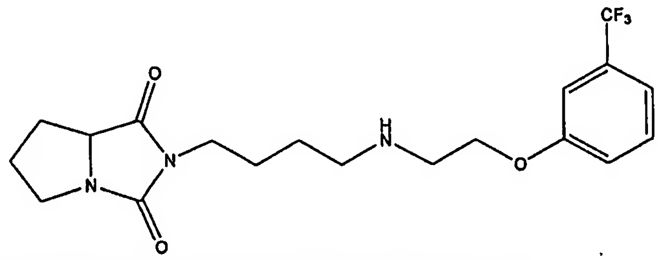
^{13}C-RMN ($CDCl_3$, δ): 22.1, 22.2 (CH_3), 25.8, 27.0, 27.5 (-$(CH_2)_2$-, C_6, C_7), 38.7 (NCH_2), 45.5 (C_5), 48.7, 49.0 ($2CH_2NH$), 63.3 (C_{7a}), 68.7 (OCH_2), 72.1 (OCH), 115.5, 116.7, 117.6, 121.8 ($C_{6'}$, $C_{4'}$, $C_{3'}$, $C_{5'}$), 145.5 ($C_{2'}$), 151.2 ($C_{1'}$), 160.3 (C_3), 173.9 (C_1).

Analysis calculated for $C_{20}H_{29}N_3O_3.HCl.H_2O$:

C, 58.03; H, 7.79; N, 10.15

Found: C, 57.92; H, 7.91; N, 10.12

Example 23. *2-[4-[2-[m-(Trifluoromethyl)phenoxy]ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole,* (w).



Chromatography: ethyl acetate/ethanol, 9:1.

Yield: 30%.

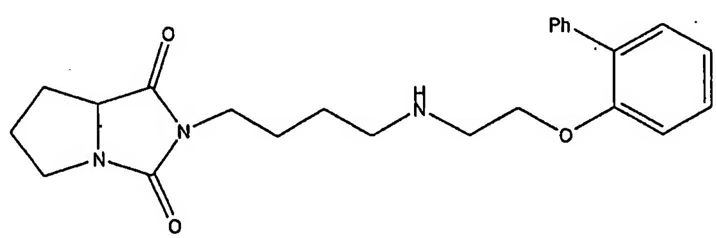
<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.50-1.72 (m, 5H, -(CH_2)$_2$-, H_7), 1.91-2.21 (m, 3H, $2H_6$, H_7), 2.72 (t, 2H, J = 6.8 Hz, C<u>H</u>$_2$NH), 3.01 (t, 2H, J = 5.2 Hz, C<u>H</u>$_2$NH), 3.11-3.22 (m, 1H, H_5), 3.42 (t, 2H, J = 6.8 Hz, NCH_2), 3.58-3.67 (m, 1H, H_5), 3.96-4.29 (m, 3H, OCH_2, H_{7a}), 7.05-7.17 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$), 7.32 (t, 1H, J = 7.9 Hz, $H_{5'}$).

<u>Analysis calculated for $C_{19}H_{24}F_3N_3O_3$.HCl.H_2O</u>:

C, 50.28; H, 6.00; N, 9.26

<u>Found</u>: C, 50.62; H, 6.10; N, 8.75

Example 24. *2-[4-[2-(1,1'-Biphenyl-2-yloxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole,* (x).



Chromatography: ethyl acetate/ethanol, 9:1.

Yield: 35%.

<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.22-1.77 (m, 4H, -(CH_2)$_2$-)), 1.93-2.08 (m, 3H, $2H_6$, H_7), 2.16-2.30 (m, 1H, H_7), 2.57 (t, 2H, J = 7.0 Hz, C<u>H</u>$_2$NH), 2.95 (t, 2H, J = 5.1 Hz, C<u>H</u>$_2$NH), 3.12-3.21 (m, 1H, H_5), 3.37 (t, 2H, J = 7.0 Hz, NCH_2), 3.53-3.62 (m, 1H, H_5), 3.96-4.05 (m, 3H, OCH_2, H_{7a}), 6.79-7.00 (m, 2H, ArH), 7.18-7.47 (m, 7H, ArH).

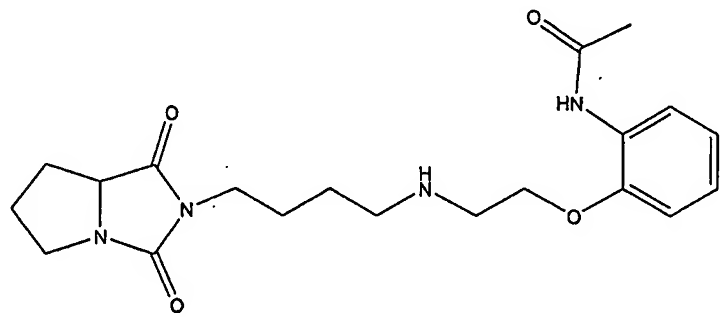
<u>^{13}C-RMN ($CDCl_3$, δ)</u>: 25.7, 26.9, 27.0, 27.5 (-(CH_2)$_2$-, C_6, C_7), 38.7 (NCH_2), 45.5 (C_5), 48.5, 48.9 ($2CH_2NH$), 63.3 (C_{7a}), 68.1 (OCH_2), 113.3 ($C_{6'}$), 121.3 ($C_{4'}$), 126.9, 128.6 ($C_{3'}$, $C_{5'}$), 127.9, 129.5, 130.8 (5CH-Ph), 131.4 ($C_{2'}$), 138.5 (C-Ph), 155.7 ($C_{1'}$), 160.8 (C_3), 173.9 (C_1).

Analysis calculated for $C_{24}H_{29}N_3O_3.HCl.6H_2O$:

C, 52.21; H, 7.67; N, 7.61

Found: C, 52.61; H, 7.27; N, 8.01

Example 25. *2-[4-[2-[o-(Acetylamino)phenoxy]ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole,* (y).



Chromatography: ethyl acetate/ethanol, 9:1.

Yield: 24%.

^{1}H-RMN ($CDCl_3$, δ): 1.60-1.71 (m, 5H, -$(CH_2)_2$-, H_7), 1.96-2.17 (m, 3H, $2H_6$, H_7), 2.21 (s, 3H, CH_3), 2.78 (t, 2H, J = 6.9 Hz, C$\underline{H}_2$NH), 3.09 (t, 2H, J = 4.9 Hz, C$\underline{H}_2$NH), 3.14-3.26 (m, 1H, H_5), 3.43 (t, 2H, J = 7.1 Hz, NCH_2), 3.62 (dt, 1H, J = 11.2, 7.8 Hz, H_5), 3.93-4.19 (m, 3H, OCH_2, H_{7a}), 6.82-6.99 (m, 3H, ArH), 8.14 (dd, 1H, J = 7.3, 1.7 Hz, ArH), 8.68 (br s, 1H, NH).

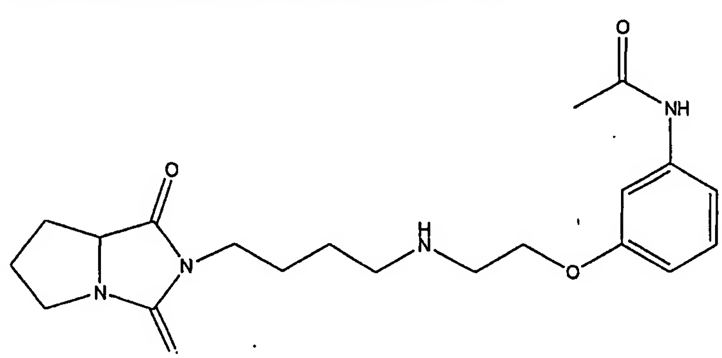
^{13}C-RMN ($CDCl_3$, δ): 24.6 (CH_3), 25.2, 25.3, 26.9, 27.4 (-$(CH_2)_2$-, C_6, C_7), 38.0 (NCH_2), 45.3 (C_5), 47.7, 48.2 ($2CH_2NH$), 63.2 (C_{7a}), 66.8 (OCH_2), 112.2 ($C_{6'}$), 121.5, 121.7 ($C_{3'}$, $C_{4'}$), 124.0 ($C_{5'}$), 128.1 ($C_{2'}$), 147.4 ($C_{1'}$), 160.6 (C_3), 169.0 (CONH), 173.9 (C_1).

Analysis calculated for $C_{20}H_{28}N_4O_4.HCl.3H_2O$:

C, 50.15; H, 7.37; N, 11.70

Found: C, 50.55; H, 7.75; N, 11.98

Example 26. *2-[4-[2-[m-(Acetylamino)phenoxy]ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole,* (z).



Chromatography: ethyl acetate/methanol, 9:1.

Yield: 31%·

^{1}H-RMN ($CDCl_3$, δ): 1.60-1.72 (m, 5H, -$(CH_2)_2$-, H_7), 1.96-2.15 (m, 3H, $2H_6$, H_7), 2.21 (s, 3H, CH_3), 2.82 (t, 2H, J = 6.1 Hz, C$\underline{H}_2$NH), 3.08 (t, 2H, J = 5.8 Hz, C$\underline{H}_2$NH), 3.19 (ddd, 1H, J = 11.2, 7.6, 5.1 Hz, H_5), 3.44 (t, 2H, J = 6.9 Hz, NCH_2), 3.62 (dt, 1H, J = 11.2, 7.8 Hz, H_5), 4.00-4.10 (m, 3H, OCH_2, H_{7a}), 4.54 (br s, 1H, NH), 6.54-6.57 (m, 1H, ArH), 6.97-7.19 (m, 3H, ArH).

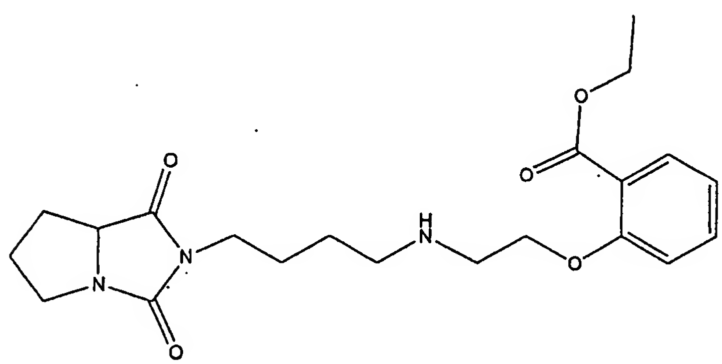
^{13}C-RMN ($CDCl_3$, δ): 24.7 (CH_3), 25.4, 25.9, 27.2, 27.6 (-$(CH_2)_2$-, C_6, C_7), 38.5 (NCH_2), 45.6 (C_5), 48.6, 48.8 ($2CH_2NH$), 63.5 (C_{7a}), 65.6 (OCH_2), 106.8 ($C_{2'}$), 110.2 ($C_{6'}$), 113.1 ($C_{4'}$), 129.9 ($C_{5'}$), 138.6 ($C_{3'}$), 158.7 ($C_{1'}$), 160.9 (C_3), 169.4 (CONH), 174.2 (C_1).

Analysis calculated for $C_{20}H_{28}N_4O_4.HCl.3H_2O$:

C, 50.15; H, 7.37; N, 11.70

Found: C, 50.65; H, 7.65; N, 12.03

Example 27. *2-[4-[2-[o-(Ethoxycarbonyl)phenoxy]ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole,* (aa).



Chromatography: ethyl acetate/ethanol, 9:1.

Yield: 25%·

^{1}H-RMN ($CDCl_3$, δ): 1.39 (t, J = 7.2 Hz, C$\underline{H}_3$CH$_2$), 1.66-1.83 (m, 5H, -$(CH_2)_2$-, H_7), 1.94-2.45 (m, 5H, $2H_6$, H_7, C$\underline{H}_2$NH), 3.15-3.27 (m, 3H, C$\underline{H}_2$NH, H_5), 3.44-3.54 (m, 2H, NCH_2), 3.66 (dt, 1H, J = 11.2, 7.6 Hz, H_5), 4.07 (dd, 1H, J = 9.0, 7.3 Hz, H_{7a}), 4.33 (q, 2H, J = 7.1 Hz, CH$_3$C$\underline{H}_2$), 4.54 (t, 2H, J = 4.6 Hz, OCH_2), 7.01-7.11 (m, 2H, ArH), 7.50 (td, 1H, J = 7.8, 1.7 Hz, ArH), 7.84 (dd, 1H, J = 7.8, 1.5 Hz, ArH).

^{13}C-RMN ($CDCl_3$, δ): 14.0 ($\underline{C}$H$_3$CH$_2$), 22.9, 24.8, 26.9, 27.4 (-$(CH_2)_2$-, C_6, C_7), 37.5 (NCH_2), 45.3 (C_5), 47.3, 47.4 ($2CH_2NH$), 61.5 (CH$_3\underline{C}$H$_2$), 63.2 (C_{7a}), 65.7

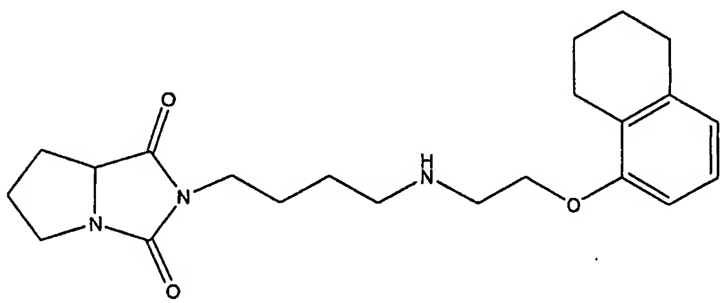
(OCH_2), 116.2 ($C_{6'}$), 120.2 ($C_{2'}$), 122.3 ($C_{4'}$), 131.6 ($C_{3'}$), 134.4 ($C_{5'}$), 158.0 ($C_{1'}$), 160.4 (C_3), 166.6 (COO), 173.8 (C_1).

Analysis calculated for $C_{21}H_{29}N_3O_5.HCl.3H_2O$:

C, 51.06; H, 7.35; N, 8.51

Found: C, 51.36; H, 7.42; N, 8.68

Example 28. *2-[4-[2-(5,6,7,8-Tetrahydronaphth-1-yloxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole,* (bb).



Chromatography: ethyl acetate/ethanol, 9:1.

Yield: 32%·

^{1}H-RMN ($CDCl_3$, δ): 1.52-1.77 (m, 9H, $-(CH_2)_4-$, H_7), 1.98-2.15 (m, 2H, $2H_6$), 2.17-2.29 (m, 1H, H_7), 2.64-2.78 (m, 6H, $C\underline{H_2}NH$, $2CH_2Ar$), 3.01 (t, J = 5.1 Hz, $C\underline{H_2}NH$), 3.17-3.29 (m, 1H, H_5), 3.49 (t, 2H, J = 7.1 Hz, NCH_2), 3.65 (dt, 1H, J = 11.2, 7.6 Hz, H_5), 4.02-4.10 (m, 3H, OCH_2, H_{7a}), 6.57 (d, 1H, J = 8.1 Hz, ArH), 6.62 (d, 1H, J = 7.6 Hz, ArH), 7.03 (t, 1H, J = 7.8 Hz, ArH).

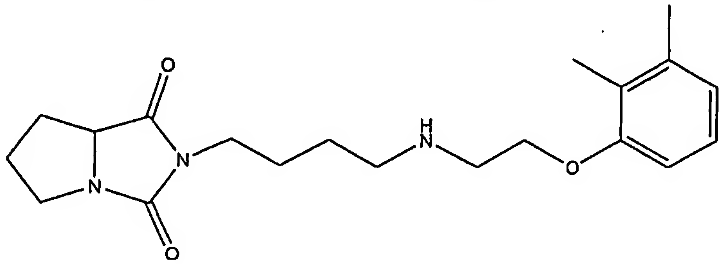
^{13}C-RMN ($CDCl_3$, δ): 22.8, 23.1, 25.8, 27.0, 27.2, 27.6 ($-(CH_2)_2-$, $-(CH_2)_4-$, C_6, C_7), 38.8 (NCH_2), 45.5 (C_5), 48.8, 49.1 ($2CH_2NH$), 63.3 (C_{7a}), 67.1 (OCH_2), 107.9 ($C_{2'}$), 121.6 ($C_{4'}$), 125.6 ($C_{3'}$), 126.1 ($C_{8'a}$), 138.6 ($C_{4'a}$), 156.5 ($C_{1'}$), 160.8 (C_3), 173.9 (C_1).

Analysis calculated for $C_{22}H_{31}N_3O_3.HCl.3H_2O$:

C, 55.51; H, 8.05; N, 8.83

Found: C, 55.18; H, 7.77; N, 8.90

Example 29. *2-[4-[2-(2,3-Dimethylphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole,* (cc).



Chromatography: ethyl acetate/methanol, 9:1.

Yield: 30%.

^{1}H-RMN ($CDCl_3$, δ): 1.53-1.73 (m, 5H, -(CH_2)$_2$-, H_7), 1.98-2.23 (m, 3H, 2H_6, H_7), 2.14 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.72 (t, 2H, J = 6.8 Hz, C$\underline{H_2}$NH), 3.02 (t, 2H, J = 4.9 Hz, C$\underline{H_2}$NH), 3.17-3.29 (m, 1H, H_5), 3.49 (t, 2H, J = 6.8 Hz, NCH_2), 3.67 (dt, 1H, J = 11.2, 7.6 Hz, H_5), 4.02-4.10 (m, 3H, OCH_2, H_{7a}), 6.70 (d, 1H, J = 8.3 Hz, ArH), 6.77 (d, 1H, J = 7.6 Hz, ArH), 7.03 (t, 1H, J = 7.8 Hz, ArH).

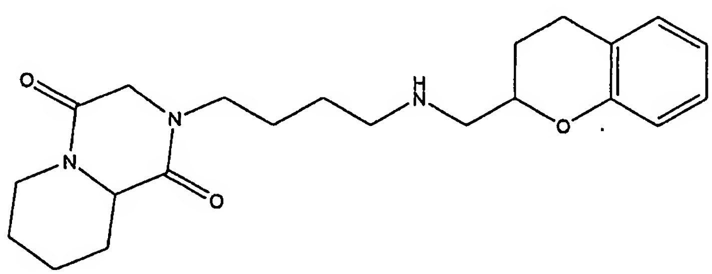
^{13}C-RMN ($CDCl_3$, δ): 11.7, 20.1 (2CH_3), 25.9, 27.0, 27.2, 27.6 (-(CH_2)$_2$-, C_6, C_7), 38.8 (NCH_2), 45.6 (C_5), 49.0, 49.2 (2CH_2NH), 63.4 (C_{7a}), 67.7 (OCH_2), 109.2 ($C_{6'}$), 122.4 ($C_{4'}$), 125.8 ($C_{5'}$), 137.9, 138.1 ($C_{2'}$, $C_{3'}$), 155.9 ($C_{1'}$), 160.5 (C_3), 173.9 (C_1).

Analysis calculated for $C_{20}H_{29}N_3O_3.HCl.3H_2O$:

C, 53.38; H, 8.06; N, 9.34

Found: C, 52.99; H, 8.15; N, 9.74

Example 30. *2-[4-[(Chroman-2-yl)methylamino]butyl]-1,4-dioxoperhydropyrido[1,2-a]pyrazine,* (dd).



Chromatography: ethyl acetate.

Yield: 35%.

^{1}H-RMN ($CDCl_3$, δ): 1.40-1.68 (m, 8H, -(CH_2)$_2$-, 2H_7, H_{8ax}, H_{9ax}), 1.96-2.07 (m, 3H, H_{8ec}, 2$H_{3'}$), 2.33-2.58 (m, 2H, H_{9ec}, H_{6ax}), 2.70-2.96 (m, 6H, 2NHC$\underline{H_2}$, 2$H_{4'}$), 3.41 (t, 2H, J = 6.6 Hz, NCH_2), 3.82 (d, 2H, J = 11.7 Hz, H_{9a}), 3.96 (s, 2H, 2H_3), 4.14-4.19 (m, 1H, $H_{2'}$), 4.67 (d, 1H, J = 12.9 Hz, H_{6ec}), 6.83 (t, 2H, J = 7.6 Hz, $H_{6'}$, $H_{8'}$), 7.02-7.11 (m, 2H, $H_{5'}$, $H_{7'}$).

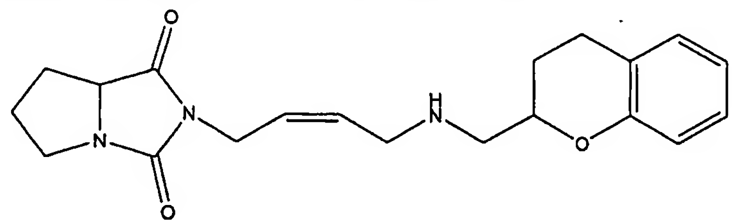
^{13}C-RMN ($CDCl_3$, δ): 24.2, 24.4, 24.6, 25.6, 26.9 (-(CH_2)$_2$-, C_7, C_8, $C_{3'}$, $C_{4'}$), 31.3 (C_9), 42.4 (C_6), 45.7 (NCH_2), 49.2, 49.3 ($NHCH_2$, C_3), 54.0 ($NHCH_2$), 59.2 (C_{9a}), 74.8 ($C_{2'}$), 116.8 ($C_{8'}$), 120.2 ($C_{6'}$), 122.0 ($C_{4a'}$), 127.2 ($C_{7'}$), 129.5 ($C_{5'}$), 154.4 ($C_{8a'}$), 161.3 (C_4), 164.9 (C_1).

Analysis calculated for $C_{22}H_{31}N_3O_3.HCl\cdot H_2O$:

C, 60.06; H, 7.79; N, 9.55

Found: C, 60.23; H, 7.43; N, 9.22

Example 31. *(Z)-2-[4-[(Chroman-2-yl)methylamino]but-2-enyl]-1,4-dioxoperhydropyrrolo[1,2-c]imidazole,* (ee).



Chromatography: ethyl acetate.

Yield: 38%.

^{1}H-RMN (CDCl$_3$, δ): 1.59-2.32 (m, 6H, 2H_6, 2H_7, 2$H_{3'}$), 2.70-2.86 (m, 4H, C$\underline{H}_2$NH, 2$H_{4'}$), 3.24 (ddd, 1H, J = 11.2, 7.6, 5.4 Hz, H_5), 3.50 (d, 2H, J = 6.6 Hz, C$\underline{H}_2$NH), 3.68 (dt, 1H, J = 11.2, 7.8 Hz, H_5), 4.03-4.19 (m, 4H, NCH_2, H_{7a}, $H_{2'}$), 5.47-5.57 (m, 1H, CH), 5.70-5.82 (m, 1H, CH), 6.79-6.86 (m, 2H, $H_{6'}$, $H_{8'}$), 7.02-7.07 (m, 2H, $H_{5'}$, $H_{7'}$).

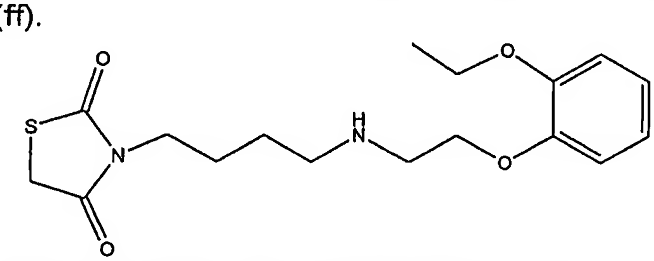
^{13}C-RMN (CDCl$_3$, δ): 24.5, 25.4, 26.8, 27.3 ($C_{3'}$, $C_{4'}$, C_6, C_7), 35.7 (NCH_2), 45.3, 45.9 (C_5, CH_2NH), 53.6 (CH_2NH), 63.2 (C_{7a}), 75.0 (C_2), 116.6 ($C_{8'}$), 119.9 ($C_{6'}$), 121.8 ($C_{4'a}$), 124.3 (CH), 127.0 ($C_{7'}$), 129.3 ($C_{5'}$), 132.7 (CH), 155.8 ($C_{8'a}$), 156.2 (C_3), 172.4 (C_1).

Analysis calculated for $C_{20}H_{25}N_3O_3 \cdot HCl \cdot 4H_2O$:

C, 51.78; H, 7.39; N, 9.06

Found: C, 51.42; H, 7.02; N, 8.75

Example 32. *3-[4-[2-(o-Ethoxyphenoxy)ethylamino]butyl]-2,4-dioxothiazolidine,* (ff).



Chromatography: ethyl acetate/ethanol, 9:1.

Yield: 55%; m.p. 70-74 ºC.

^{1}H-RMN (CDCl$_3$, δ): 1.44 (t, 3H, J = 7.0 Hz, CH_3), 1.57-1.74 (m, 4H, -$(CH_2)_2$-), 2.83 (t, 2H, J = 7.0 Hz, C$\underline{H}_2$NH), 3.13 (t, 2H, J = 5.0 Hz, C$\underline{H}_2$NH), 3.29 (t, 2H, J

= 7.5 Hz, NCH_2), 3.96 (s, 2H, $2H_5$), 4.08 (q, 2H, J = 7.0 Hz, $C\underline{H}_2CH_3$), 4.19 (t, 2H, J = 5.0 Hz, OCH_2), 6.86-6.97 (m, 4H, ArH).

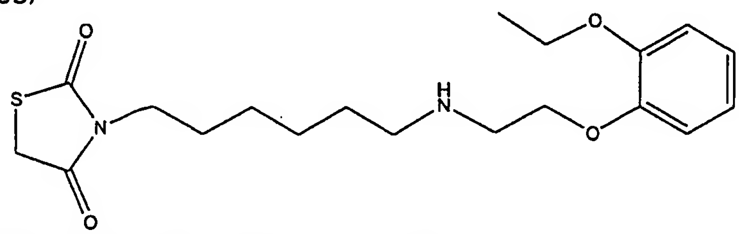
<u>^{13}C-RMN ($CDCl_3$, δ)</u>: 14.9 (CH_3), 24.0, 25.2 ($-(CH_2)_2-$), 33.8 (C_5), 41.6 (NCH_2), 48.2, 48.5 ($2CH_2NH$), 64.4 ($\underline{C}H_2CH_3$), 68.3 (OCH_2), 113.6, 115.1, 121.0, 121.8 ($C_{6'}$, $C_{4'}$, $C_{3'}$, $C_{5'}$), 148.3, 149.1 ($C_{1'}$, $C_{2'}$), 171.3 (C_2, C_4).

<u>Analysis calculated for $C_{17}H_{24}N_2O_4S.HCl\cdot 1/2H_2O$</u>:

C, 51.31; H, 6.59; N, 7.04

<u>Found</u>: C, 51.36; H, 7.04; N, 6.66

Example 33. *3-[6-[2-(o-Ethoxyphenoxy)ethylamino]hexyl]-2,4-dioxothiazolidine*, (gg).



Chromatography: ethyl acetate/ethanol, 9:1.

Yield: 48%; m.p. 92-94 °C.

<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.18-1.66 (m, 11H, $-(CH_2)_4-$, CH_3), 2.73 (t, 2H, J = 7.1 Hz, $C\underline{H}_2NH$), 3.06 (t, 2H, J = 5.3 Hz, $C\underline{H}_2NH$), 3.46 (br s, 1H, NH), 3.60 (t, 2H, J = 7.4 Hz, NCH_2), 3.92 (s, 2H, $2H_5$), 4.06 (q, 2H, J = 7.0 Hz, $C\underline{H}_2CH_3$), 4.15 (t, 2H, J = 5.0 Hz, OCH_2), 6.81-6.97 (m, 4H, ArH).

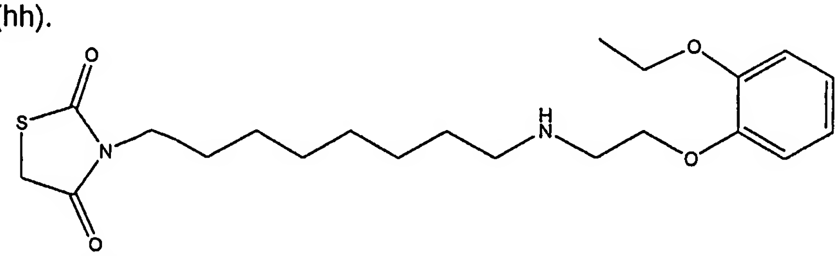
<u>^{13}C-RMN ($CDCl_3$, δ)</u>: 14.8 (CH_3), 26.3, 26.6, 27.3, 29.1 ($-(CH_2)_4-$), 33.6 (C_5), 41.9 (NCH_2), 48.4, 49.2 ($2CH_2NH$), 64.4 ($\underline{C}H_2CH_3$), 68.3 (OCH_2), 113.6, 115.1, 121.0, 121.8 ($C_{6'}$, $C_{4'}$, $C_{3'}$, $C_{5'}$), 148.3, 149.1 ($C_{1'}$, $C_{2'}$), 171.3 (C_2, C_4).

<u>Analysis calculated for $C_{19}H_{28}N_2O_4S.HCl\cdot H_2O$</u>:

C, 52.46; H, 7.18; N, 6.44

<u>Found</u>: C, 52.64; H, 6.99; N, 6.45

Example 34. *3-[8-[2-(o-Ethoxyphenoxy)ethylamino]octyl]-2,4-dioxothiazolidine*, (hh).



Chromatography: ethyl acetate/ethanol, 9:1.

Yield: 48%; m.p. 105-108 °C.

<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.07-1.54 (m, 15H, -$(CH_2)_6$-, CH_3), 2.73 (t, 2H, J = 7.4 Hz, C<u>H</u>$_2$NH), 3.04 (t, 2H, J = 5.2 Hz, C<u>H</u>$_2$NH), 3.44 (br s, 1H, NH), 3.54 (t, 2H, J = 7.4 Hz, NCH_2), 3.87 (s, 2H, $2H_5$), 4.01 (q, 2H, J = 7.0 Hz, C<u>H</u>$_2$CH$_3$), 4.13 (t, 2H, J = 5.2 Hz, OCH_2), 6.76-6.92 (m, 4H, ArH).

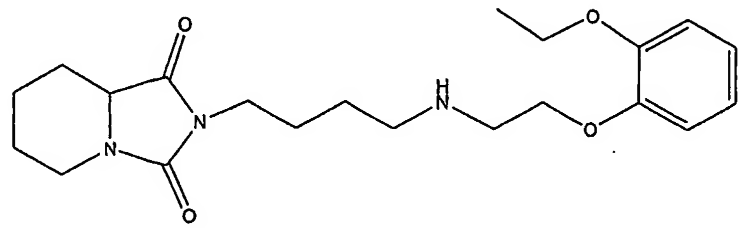
<u>^{13}C-RMN ($CDCl_3$, δ)</u>: 14.7 (CH_3), 26.4, 26.8, 27.3, 28.7, 28.8, 29.0 (-$(CH_2)_6$-), 33.5 (C_5), 41.9 (NCH_2), 48.1, 49.1 ($2CH_2NH$), 64.3 (<u>C</u>H$_2$CH$_3$), 68.0 (OCH_2), 113.5, 115.1, 120.9, 121.9 ($C_{6'}$, $C_{4'}$, $C_{3'}$, $C_{5'}$), 148.3, 149.2 ($C_{1'}$, $C_{2'}$), 171.3 (C_2, C_4).

<u>Analysis calculated for $C_{21}H_{32}N_2O_4S.HCl\cdot1/2H_2O$</u>:

C, 55.55; H, 7.55; N, 6.17

<u>Found</u>: C, 55.78; H, 7.34; N, 6.04

Example 35. *2-[4-[2-(o-Ethoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydroimidazo[1,5-a]pyridine,* (ii).



Chromatography: ethyl acetate/ethanol, 7:3.

Yield: 31%.

<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.28-1.74 (m, 11H, -$(CH_2)_2$-, CH_3, H_{6ax}, H_{7ax}, H_{8ax}, H_{6ec}), 1.94-2.03 (m, 1H, H_{7ec}), 2.14-2.21 (m, 1H, H_{8ec}), 2.73-2.87 (m, 3H, H_{5ax}, C<u>H</u>$_2$NH), 3.11 (t, 2H, J = 5.2 Hz, C<u>H</u>$_2$NH), 3.51 (t, 2H, J = 6.5 Hz, NCH_2), 3.69-3.79 (m, 1H, H_{8a}), 4.00-4.12 (m, 3H, C<u>H</u>$_2$CH$_3$, H_{5ec}), 4.18 (t, 2H, J = 5.1 Hz, OCH_2), 6.77-6.87 (m, 4H, ArH).

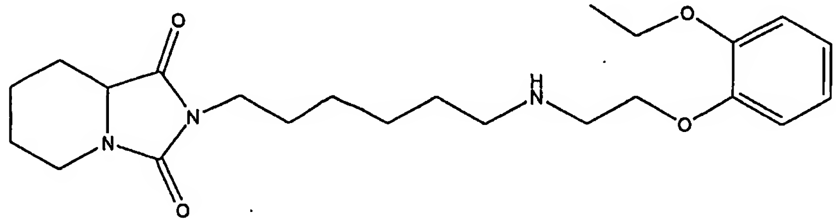
<u>^{13}C-RMN ($CDCl_3$, δ)</u>: 15.1 (CH_3), 22.9, 25.1, 26.0, 27.9, 29.8 (-$(CH_2)_2$-, C_6, C_7, C_8), 38.3 (NCH_2), 39.4 (C_5), 48.3, 48.8 ($2CH_2NH$), 57.5 (C_{8a}), 64.6, 68.1 (<u>C</u>H$_2$CH$_3$, OCH_2), 113.7, 115.4, 121.2, 122.2 ($C_{6'}$, $C_{4'}$, $C_{3'}$, $C_{5'}$), 148.3, 149.3 ($C_{1'}$, $C_{2'}$), 154.1 (C_3), 173.4 (C_1).

<u>Analysis calculated for $C_{21}H_{31}N_3O_4.HCl\cdot H_2O$</u>:

C, 56.81; H, 7.72; N, 9.46

<u>Found</u>: C, 57.38; H, 8.00; N, 9.02

Example 36. *2-[6-[2-(o-Ethoxyphenoxy)ethylamino]hexyl]-1,3-dioxoperhydroimidazo[1,5-a]pyridine,* (jj).



Chromatography: ethyl acetate/ethanol, 8:2.

Yield: 49%.

<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.23-1.63 (m, 14H, -$(CH_2)_4$-, CH_3, H_{6ax}, H_{7ax}, H_{8ax}), 1.71-1.75 (m, 1H, H_{6ec}), 1.96-2.01 (m, 1H, H_{7ec}), 2.18-2.22 (m, 1H, H_{8ec}), 2.70 (t, 2H, J = 7.3 Hz, C<u>H</u>$_2$NH), 2.77-2.87 (m, 1H, H_{5ax}), 3.03 (t, 2H, J = 5.3 Hz, C<u>H</u>$_2$NH), 3.48 (t, 2H, J = 7.3 Hz, NCH_2), 3.73 (dd, 1H, J = 11.9, 4.1 Hz, H_{8a}), 4.07 (q, 2H, J = 7.0 Hz, C<u>H</u>$_2$CH$_3$), 4.14 (t, 2H, J = 5.3 Hz, OCH_2), 4.18-4.19 (m, 1H, H_{5ec}), 6.86-7.26 (m, 4H, ArH).

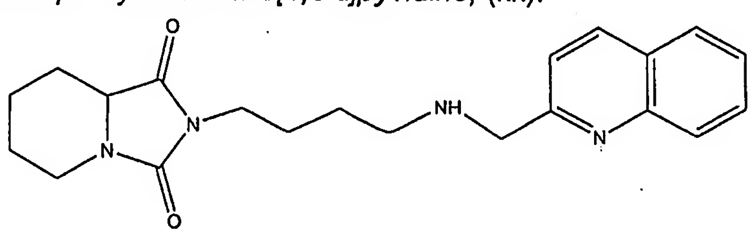
<u>^{13}C-RMN ($CDCl_3$, δ)</u>: 14.7 (CH_3), 22.6, 24.8, 26.3, 26.6, 27.6, 27.0, 29.3 (-$(CH_2)_4$-, C_6, C_7, C_8), 38.3 (NCH_2), 39.1 (C_5), 48.4, 49.3 (2CH_2NH), 57.1 (C_{8a}), 64.3, 68.4 (<u>C</u>H$_2$CH$_3$, OCH_2), 113.5, 114.9, 120.9, 121.6 ($C_{6'}$, $C_{4'}$, $C_{3'}$, $C_{5'}$), 148.3, 148.7 ($C_{1'}$, $C_{2'}$), 154.4 (C_3), 173.1 (C_1).

<u>Analysis calculated for $C_{23}H_{35}N_3O_4$.HCl.7/2H_2O</u>:

C, 53.43; H, 8.38; N, 8.13

<u>Found</u>: C, 53.18; H, 7.82; N, 7.60

Example 37. *2-[4-[(2-Quinolyl)methylamino]butyl]-1,3-dioxoperhydroimidazo[1,5-a]pyridine,* (kk).



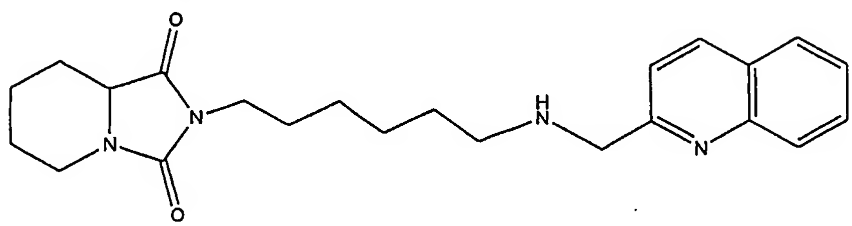
Chromatography: ethyl acetate/ethanol, 7:3.

Yield: 45%; m.p. 206-208 ºC.

<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.21-1.77 (m, 8H, -$(CH_2)_2$-, H_{6ax}, H_{7ax}, H_{8ax}, H_{6ec}), 1.95-1.99 (m, 1H, H_{7ec}), 2.16-2.22 (m, 1H, H_{8ec}), 2.76-2.86 (m, 3H, H_{5ax}, C<u>H</u>$_2$NH), 3.24 (br s, 1H, NH), 3.53 (t, 2H, J = 6.9 Hz, NCH_2), 3.73 (dd, 1H, J = 12.1, 4.4 Hz, H_{8a}), 4.12-4.18 (m, 3H, CH_2Ar, H_{5ec}), 7.46 (d, 1H, J = 8.4 Hz, $H_{3'}$), 7.44-7.54 (m, 1H,

$H_{6'}$), 7.67-7.73 (m, 1H, $H_{7'}$), 7.81 (dd, 1H, J = 8.2, 1.1 Hz, $H_{5'}$), 8.06 (d, J = 8.5 Hz, 1H, $H_{4'}$), 8.13 (d, 1H, J = 8.5 Hz, $H_{8'}$).
<u>^{13}C-RMN ($CDCl_3$, δ)</u>: 22.7, 24.9, 25.9, 26.3, 27.8 (-$(CH_2)_2$-, C_6, C_7, C_8), 38.2 (NCH_2), 39.3 (C_5), 48.7 (CH_2NH), 54.6 (CH_2Ar), 57.3 (C_{8a}), 120.4 ($C_{3'}$), 126.3 ($C_{6'}$), 127.3, 127.5 ($C_{5'}$, $C_{8'}$), 128.9. 129.6 ($C_{4'}$, $C_{7'}$), 136.7 ($C_{4'a}$), 147.5 ($C_{8'a}$), 154.5 ($C_{2'}$), 158.0 (C_3), 173.2 (C_1).
<u>Analysis calculated for $C_{21}H_{26}N_4O_2$.2HCl.1/2H_2O</u>:
C, 56.25; H, 6.52; N, 12.50
<u>Found</u>: C, 56.66; H, 6.53; N, 11.94

Example 38. *2-[6-[(2-Quinolyl)methylamino]hexyl]-1,3-dioxoperhydroimidazo[1,5-a]pyridine* (II).



Chromatography: ethyl acetate/methanol, 7:3.
Yield: 30%; m.p. 176-188 °C.
<u>^{1}H-RMN ($CDCl_3$, δ)</u>: 1.19-1.74 (m, 12H, -$(CH_2)_4$-, H_{6ax}, H_{7ax}, H_{8ax}, H_{6ec}), 1.95-2.00 (m, 1H, H_{7ec}), 2.17-2.22 (m, 1H, H_{8ec}), 2.76 (t, 2H, J = 7.1 Hz, $C\underline{H_2}NH$), 2.81-2.86 (m, 1H, H_{5ax}), 3.06 (br s, 1H, NH), 3.48 (t, 2H, J = 7.3 Hz, NCH_2), 3.72 (dd, 1H, J = 11.9, 4.3 Hz, H_{8a}), 4.14-4.19 (m, 3H, CH_2Ar, H_{5ec}), 7.46 (d, 1H, J = 8.5 Hz, $H_{3'}$), 7.49-7.55 (m, 1H, $H_{6'}$), 7.68-7.74 (m, 1H, $H_{7'}$), 7.81 (dd, 1H, J = 8.2, 1.1 Hz, $H_{5'}$), 8.06 (d, J = 8.5 Hz, 1H, $H_{4'}$), 8.13 (d, 1H, J = 8.4 Hz, $H_{8'}$).
<u>^{13}C-RMN ($CDCl_3$, δ)</u>: 22.7, 24.9, 26.3, 26.6, 27.8, 28.0, 29.0 (-$(CH_2)_4$-, C_6, C_7, C_8), 38.4 (NCH_2), 39.2 (C_5), 49.2 (CH_2NH), 54.6 (CH_2Ar), 57.2 (C_{8a}), 120.3 ($C_{3'}$), 126.2 ($C_{6'}$), 127.3, 127.5 ($C_{5'}$, $C_{8'}$), 128.9, 129.6 ($C_{4'}$, $C_{7'}$), 136.7 ($C_{4'a}$), 147.5 ($C_{8'a}$), 154.5 ($C_{2'}$), 158.2 (C_3), 173.2 (C_1).
<u>Analysis calculated for $C_{23}H_{30}N_4O_2$.2HCl.3/2H_2O</u>:
C, 55.87; H, 7.13; N, 11.33
<u>Found</u>: C, 55.77; H, 7.09; N, 10.77

Example 39. Radioligand binding assays.

The <u>in vitro</u> affinity of the compounds of the present invention for the 5-

HT_{1A}, 5-HT_{2A}, 5-HT_3, 5-HT_4, 5-HT_7, α_1 and D_2 cerebral receptors was evaluated using radioligand binding assays. The following specific ligands and tissues were used:

* 5-HT_{1A} receptors, [^{3}H]-8-OH-DPAT, rat cerebral cortex;
* 5-HT_{2A} receptors, [^{3}H]ketanserin, rat cerebral cortex;
* 5-HT_3 receptors, [^{3}H]LY 278584, rat cerebral cortex;
* 5-HT_4 receptors, [^{3}H]GR 113808, rat striatum;
* 5-HT_7 receptors, [^{3}H]-5-CT, rat hypothalamus;
* α_1 receptors, [^{3}H]prazosin, rat cerebral cortex;
* D_2 receptors, [^{3}H]spiperone, rat striatum.

Compound BAYx3702 was selected as a 5-HT_{1A} reference ligand, as well as the left-hand isomer of the same, (-)-BAYx3702.

For all receptor binding assays, male Sprague-Dawley rats (*Rattus norvegicus albinus*), weighing 180-200 g, were killed by decapitation and the brains rapidly removed and dissected. Tissues were stored at -80 °C for subsequent use and homogenized on a Polytron PT-10 homogenizer. Membrane suspensions were centrifuged on a Beckman J2-HS instrument.

The bonded radioactive ligands were separated from the free ones by vacuum filtration on Whatman GF/C filters washed twice with 4 mL of the corresponding buffer. 4 mL of liquid scintillation (EcoLite) were added and the radioactivity bonded to the membranes was measured by liquid scintillation spectrometry.

5-HT_{1A} receptor

Binding assays were performed by a modification of the procedure previously described by Clark et al. (J. Med. Chem., 1990, 33, 633), as described below.

The cerebral cortex was homogenized in 10 volumes of ice-cold Tris buffer (50 mM Tris-HCl, pH 7.7 at 25 °C) and centrifuged at 28000*g* for 15 min. The membrane pellet was washed twice by resuspension and centrifugation. After the second wash the resuspended pellet was incubated at 37 °C for 10 min. Membranes were then collected by centrifugation and the final pellet was resuspended in 50 mM Tris-HCl, 5 mM $MgSO_4$, and 0.5 mM EDTA buffer (pH

7.4 at 37 °C). Fractions of 100 μL of the final membrane suspension (about 1 mg of protein) were incubated at 37 °C for 15 min with 0.6 nM [^{3}H]-8-OH-DPAT (133 Ci/mmol), in the presence or absence of the competing drug, in a final volume of 1.1 mL of assay buffer (50 mM Tris-HCl, 10 nM clonidine, 30 nM prazosin, pH 7.4 at 37 °C). Nonspecific binding was determined with 10 μM 5-HT.

5-HT_{2A} receptor

Binding assays were performed by a modification of the procedure previously described by Titeler et al. (Biochem. Pharmacol., 1987, 36, 3265), as described below.

The frontal cortex was homogenized in 60 volumes of ice-cold buffer (50 mM Tris-HCl, 0.5 mM Na_2EDTA, 10 mM $MgSO_4$, pH 7.4 at 25 °C), and centrifuged at 30000*g* for 15 min at 4 °C. The membrane pellet was washed by resuspension and centrifugation. After the second wash the resuspended pellet was incubated at 37 °C for 10 min. Membranes were then collected by centrifugation and the final pellet was resuspended in 10 volumes of assay buffer (50 mM Tris-HCl, 0.5 mM Na_2EDTA, 10 mM $MgSO_4$, 0.1% ascorbic acid, 10 μM pargyline, pH 7.4 at 25 °C). Fractions of 100 μL of the final membrane suspension (about 5 mg/mL of protein) were incubated at 37 °C for 15 min with 0.4 nM [^{3}H]ketanserin, in the presence or absence of the competing drug, in a final volume of 2 mL of assay buffer. Nonspecific binding was determined with 1 μM cinanserin.

5-HT_3 receptor

Binding assays were performed by a modification of the procedure previously described by Wong et al. (Eur. J. Pharmacol., 1989, 166, 107), as described below.

The cerebral cortex was homogenized in 9 volumes of ice-cold 0.32 M sucrose and centrifuged at 1000*g* for 10 min at 4 °C. The supernatant was centrifuged at 17000*g* for 20 min at 4 °C. The membrane pellet was washed twice by resuspension in 60 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.4 at 25 °C) and centrifugation at 48000*g* for 10 min at 4 °C. After the second

wash the resuspended pellet was incubated at 37 °C for 10 min, and centrifuged at 48000*g* for 10 min at 4 °C. Membranes were resuspended in 2.75 volumes of assay buffer (50 mM Tris-HCl, 10 μM pargyline, 0.6 mM ascorbic acid, and 5 mM $CaCl_2$, pH 7.4 at 25 °C). Fractions of 100 μL of the final membrane suspension (about 2 mg/mL of protein) were incubated at 25 °C for 30 min with 0.7 nM [^{3}H]LY 278584, in the presence or absence of the competing drug, in a final volume of 2 mL of assay buffer. Nonspecific binding was determined with 10 μM 5-HT.

5-HT_4 receptor

Binding assays were performed by a modification of the procedure previously described by Grossman et al. (Br. J. Pharmacol., 1993, 109, 618), as described below.

The striatum was homogenized in 15 volumes of ice-cold 50 mM HEPES buffer (pH 7.4 at 4 °C) and centrifuged at 48000*g* for 10 min. The pellet was resuspended in 20 volumes of assay buffer (50 mM HEPES, pH 7.4 at 25 °C). Fractions of 100 μL (about 5 mg/mL of protein) of the final membrane suspension were incubated at 37 °C for 30 min with 0.1 nM [^{3}H]GR 113808, in the presence or absence of the competing drug, in a final volume of 1 mL of assay buffer. Nonspecific binding was determined with 30 μM 5-HT.

5-HT_7 receptor

Binding assays were performed by a modification of the procedure previously described by Aguirre et al. (Eur. J. Pharmacol., 1998, 346, 181), as described below.

The hypothalamus was homogenized in 5 mL of ice-cold Tris buffer (50 mM Tris-HCl, pH 7.4 at 25 °C) and centrifuged at 48000*g* for 10 min. The membrane pellet was washed by resuspension and centrifugation, and then the resuspended pellet was incubated at 37 °C for 10 min. Membranes were then collected by centrifugation and the final pellet was resuspended in 100 volumes of ice-cold 50 mM Tris-HCl, 4 mM $CaCl_2$, 1 mg/mL ascorbic acid, 0.01 mM pargyline and 3 μM pindolol buffer (pH 7.4 at 25 °C). Fractions of 400 μL of the final membrane suspension were incubated at 23 °C for 120 min. with 0.5 nM

[3H]-5-CT (88 Ci/mmol), in the presence or absence of several concentrations of the competing drug, in a final volume of 0.5 mL of assay buffer (50 mM Tris-HCl, 4 mM $CaCl_2$, 1 mg/mL ascorbic acid, 0.01 mM pargyline and 3 μM pindolol buffer (pH 7.4 at 25 °C)). Non-specific binding was determined with 10 μM 5-HT.

α_1 receptor

Binding assays were performed by a modification of the procedure previously described by Ambrosio et al. (Neurosci. Lett., 1984, 49, 193), as described below.

The cerebral cortex was homogenized in 20 volumes of ice-cold buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, pH 7.4 at 25 °C) and centrifuged at 30000*g* for 15 min. Pellets were washed twice by resuspension and centrifugation. Final pellets were resuspended in the same buffer. Fractions of the final membrane suspension (about 250 μg of protein) were incubated at 25 °C for 30 min with 0.2 nM [3H]prazosin (23 Ci/mmol), in the presence or absence of six concentrations of the competing drug, in a final volume of 2 mL of buffer. Nonspecific binding was determined with 10 μM phentolamine.

D_2 receptor

Binding assays were performed by a modification of the procedure previously described by Leysen et al. (Biochem. Pharmacol., 1978, 27, 307), as described below.

The striatum was homogenized in 50 mM Tris-HCl (pH 7.7 at 25 °C) and centrifuged at 48000*g* for 10 min. The pellet was resuspended and centrifuged as before. The final pellet was resuspended in 50 mM Tris-HCl (pH 7.7 at 25 °C) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, and 0.1% ascorbic acid. Fractions of the final membrane suspension (125-150 μg of protein) were incubated at 25 °C for 60 min with 0.8 nM [3H]raclopride (77 Ci/mmol), in the presence or absence of six concentrations of the competing drug, in a final volume of 1.1 mL of the assay buffer (pH 7.4 at 25 °C). Nonspecific binding was determined with 1 μM (+)-butaclamol.

For all binding assays, competing drug, nonspecific, total and radioligand bindings were defined in triplicate. Incubation was terminated by rapid vacuum filtration through Whatman GF/B filters, presoaked in 0.05% poly(ethylenimine), using a Brandel cell harvester. The filters were then washed with the assay buffer, dried and placed in poly(ethylene) vials to which were added 4 mL of a scintillation cocktail (Aquasol). The radioactivity bound to the filters was measured by liquid scintillation spectrometry. The data were analyzed by an iterative curve-fitting procedure (program Prism, Graph Pad), which provided IC_{50}, K_i, and r^2 values for test compounds, K_i values being calculated from the Cheng and Prusoff equation. The protein concentrations of the rat cerebral cortex and the rat striatum were determined by the method of Lowry, using bovine serum albumin as the standard.

Results:

All the tested compounds showed a high affinity for the 5-HT_{1A} receptor with a K_i value of between 0.5 and about 100 nM. Most of the compounds bind the 5-HT_{1A} receptor with an affinity of below 30 nM. Also, most of the compounds are highly selective for the 5-HT_{1A} receptor over 5-HT_{2A} 5-HT_3, 5-HT_4 and dopamine receptors.

Example 40. Functional characterization.

Cell culture and determination of cAMP levels after stimulation of the adenylate cyclase enzyme with forskolin.

HeLa cells transfected with the human 5-HT_{1A} receptor (HA 6 cells) were grown in 75 mL flasks containing 20 mL of Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum, 500 units penicillin and 500 µg streptomycin/mL (P/S) and 0.3 mg/mL geneticin. Forty-eight hours before the experiment cells were plated at a density of 75 x 10^3 cells in 1.5 mL of DMEM-P/S-fetal calf serum-geneticin medium in 12 multiwell plates. The day of the experiment, cells were treated with 0.5 mM 1-methyl-3-isobutylxanthine (IBMX), 10 µM forskolin, and vehicle or and different concentrations of the compounds under study in a 37 °C and 5% CO_2 incubator. Ten minutes later, treatment was stopped and cells were lysed with a 65% ethanol solution for 2 h, then the ethanol was collected and evaporated at 55 °C leaving a pellet with

cAMP. Samples were analyzed using a commercial radioimmunoassay (RIA) kit ([^{3}H]cAMP assay system, cod. TRK 432; Amersham). Protein was measured by Bradford's method. Competition binding isotherms were analysed by using an iterative curve-fitting procedure (program Origin 7.0), which provided EC_{50} values for test compounds.

The experiment shows that the tested compounds significantly inhibit the AMPc formation in HeLa cells, most compounds acting as pure and some as partial agonists.

Determination of the rectal temperature in mice.

5-HT_{1A} receptor agonists such as, for example, 8-OH-DPAT, reduce the body temperature of the rodents. This effect in the mouse seems to be due to the activation of the somatodendritic receptors (De Vry, Psychopharmacology 1995, 121, 1) since the administration for two weeks of a tryptophan hydroxylase inhibitor such as *para*chlorophenylalanine or the damage with a selective neurotoxin of serotoninergic neurons such as 5,7-dihydroxytryptamine (5,7-DHT) completely blocks the hypothermic effect on mice.

In the test carried out with the compounds of the present invention, batches of 8-10 mice were processed, testing at least 4 doses of the compounds object under study. Animals were maintained in a temperature and light (25±1 °C, light on between 8.00 a.m. and 8.00 p.m.) controlled environment. Food and tap water were provided ad libitum. All experiments were performed between 9.00 a.m. and 2.00 p.m. The test consisted of inserting a probe into the animals rectum 1.5 cm for 40 s measuring the basal temperature, this being the 0 time of the experiment. Immediately afterwards, the compounds to be tested were administered subcutaneously (s.c) and the rectal temperature was measured after different times: 15, 30, 60, 120 and 240 minutes.

The experiment shows that the tested compounds are 5-HT_{1A} agonists, according to the minimum effective dose administered and the hypothermic effect obtained.

Example 41. In vitro neuroprotection studies.

Neurotoxicity induced by hypoxia / hypoglycaemia.

The capacity to prevent neurotoxicity induced by hypoxia / hypoglycaemia in primary cultures of rat hippocampus (E18) was determined. To prepare the cultures, the foetuses' brain was dissected, separating the meninges, and the hippocampus was dispersed on a neurobasal medium supplemented with B-27. After centrifuging at 700 g, the pellet was mechanically redispersed. The density of the cellular suspension was measured and aliquots were taken to culture on Petri dishes, previously coated with poly-lysine, using the same medium. The culture was kept in an incubator at 37°C in a 95% air/ 5% CO_2 atmosphere. After 10 days' culture, the dishes were transferred, in a glucose-free medium, to a chamber wherein they were kept for 2 hours in a 95% N_2/ 5% CO_2 atmosphere. Before the hypoxia, the compounds to be studied were added at variable times and concentrations.

Neurotoxicity due to deprivation of trophic factors.

The prevention of cellular death with apoptotic characteristics which results after maintaining the hippocampus cultures in a serum-free medium for 48 hours (Koh et al., Science, 1995, 268, 573) was also studied. In this case, an Eagle medium (DMEM) modified with 10% of calf serum was initially used and, after 10 days, the cultures were transferred to the DMEM culture deprived of calf serum.

In both cases, the measurement of the mitochondrial dehydrogenase on 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) with subsequent colorimetric measurement of the formazan formed, which provides a cell survival index (Nonaka et al., Proc. Natl. Acad. Sci. USA, 1998, 95, 2642), was considered as toxicity indexes.

The results obtained are set down in the following table 1.

Table 1.

Compound	Protection (%)	
	Serum Deprivation	Oxygen-glucose deprivation
8-OH-DPAT	44.0 ± 1.4	54.0 ± 3.5
(-)-BAYx3702	31.0 ± 2.9	77.5 ± 8.6
(±)-BAYx3702	25.9 ± 2.5	ND
a	10.7 ± 2.4	55.8 ± 12.5
b	19.0 ± 3.3	42.0 ± 7.8
c	13.0 ± 4.3	65.6 ± 4.8
d	15.5 ± 2.2	78.0 ± 6.5
e	29.6 ± 2.8	78,0 ± 6,8
f	36.0 ± 3.2	35.0 ± 7.0
g	32.0 ± 4.0	32.0 ± 8.0

Example 42. In vivo neuroprotection study.

Focal ischemic model in rats.

The intraluminal occlusion of the middle cerebral artery (MCA) in rats was performed following previously described methods (Justicia et al., J Cereb. Blood Flow Metab., 1999, 19, 128), as described below.

The rats were anaesthetised with halotan, maintaining their temperature at 37.5°C using an electric blanket connected to a rectal probe and cannulating the left femoral artery to monitor blood pressure. The right carotid artery was exposed, occluding the extra-cranial branches, and a blunt nylon filament was introduced through the external carotid until reaching the level when the middle cerebral artery (MCA) branches.

The selected compounds were administered intravenously. 24 Hours after the ischemic damage, the rats were anaesthetised with ether, they were

perfused with saline solution and were then decapitated, extracting the brains that were cut into 1.5 mm coronal slices. The slices were then incubated in 4% triphenyltetrazolium chloride (TTC), which reacts with the intact mitochondrial enzymes producing a red colour which contrasts with the paleness of the infracted area, permitting it to be viewed, subsequently maintaining it in 10% formalin. The volume of cerebral infarction (mm^3) was calculated by measuring, in an image analyser, the affected area in the areas of cerebral cortex irrigated by the MCA and in the striatum and multiplying the average value obtained in each slice by the thickness thereof.

The intravenous infusion of 40 µg/Kg of compound (e) for 4 hours significantly reduced the infracted cerebral volume in the rat after intraluminal occlusion of the MCA. The effect was observed even when the rats received the compound for a period of 2 hours after the start of the MCA occlusion. The protective effect was only apparent in the cortical area but not in the subcortical area and did not cause alterations in the arterial blood pressure.

In Table 2, the values of infracted volume both for a saline solution, and for the standard (-)-BAYx3702 and for compound (e), are set down.

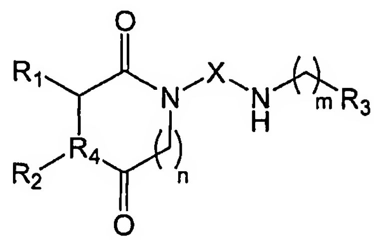
Table 2.

Compound	Dose	Infarcted Volumen (mm^3)		
		Total	Cortical	Subcortical
Saline	-	546.4 ± 51.1	399.2 ± 37.5	147.2 ± 23.4
(-)-BAY x3702	40 µg/kg	376.7 ± 57.8 *	271.2 ± 54.7 *	105.5 ± 9.3
e	40 µg/kg	386.7 ± 47.1 *	262.7 ± 40.9 *	124.0 ± 14.3

* $p<0.05$ vs. Control (saline)

CLAIMS

1. A compound of formula I:



one of their stereochemically isomer forms or a pharmaceutically acceptable salt thereof, wherein:

R_1 and R_2 are H or are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring; if R_4=S then R_1 is H and R_2 is absent;
R_4 is selected from the group consisting of N and S;
n being an integrer from 0 to 1;
X is selected from the group consisting of C_2-C_{10}-alkyl, C_2-C_{10}-alkenyl and -CH_2-Y-CH_2-; wherein Y is phenyl;
m being an integrer from 1 to 2;
R_3 is selected from the group consisting of chroman-2-yl, 2-quinolyl and -O-phenyl, wherein the aromatic ring of the chromanyl moiety, the quinolyl or the phenyl residue is optionally substituted by one or more groups chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, halogen, C_2-C_6-alkenyl, halo-(C_1-C_6)-alkyl, halo-(C_1-C_6)-alkoxy, phenyl, phenyl(C_1-C_6)-alkyl, phenoxy, C_1-C_6-alkylcarbonyl, phenylcarbonyl, phenyl(C_1-C_6)alkylcarbonyl, C_1-C_6-alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, C_1-C_6-alkylcarbonylamino, hydroxy, cyano, nitro, amino, N-(C_1-C_6)-alkylamino, N,N-(C_1-C_6)-dialkylamino, carboxy, sulfo, sulfamoyl, sulfonylamino, (C_1-C_6)alkylaminosulfonyl or (C_1-C_6)alkylsulfonylamino; or wherein the phenyl ring is substituted by two neighbouring residues, which together with the phenyl ring to which they are attached form tetrahydronaphthyl; wherein each alkyl is optionally substituted with hydroxy or amino;
provided that the compound is not 2-[4-[(chroman-2-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, 3-[4-[(chroman-2-yl)methylamino]butyl]-2,4-dioxothiazolidine, 3-[5-[(chroman-2-yl)methylamino]pentyl]-2,4-

dioxothiazolidine, 3-[6-[(chroman-2-yl)methylamino]hexyl]-2,4-dioxothiazolidine, 2-[4-[2-(phenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole or 3-[4-[2-(phenoxy)ethylamino]butyl]-2,4-dioxothiazolidine.

2. Compound according to claim 1, wherein R_3 is selected from the group consisting of chroman-2-yl, 2-quinolyl and -O-phenyl, wherein the phenyl residue is optionally substituted by a group chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, or halogen;

3. Compound according to claim 1 or 2, wherein m is 1 and R_3 is chroman-2-yl.

4. Compound according to claim 3, wherein R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring; and R_4 is N.

5. Compound according to any of claims 3 to 4, wherein X is selected from the group consisting of C_2-C_{10}-alkyl, (*E*)-2-butenyl, 3-methylbenzyl or 4-methylbenzyl.

6. Compound according to claim 3, wherein R_1 is H, R_2 is absent and R_4 is S.

7. Compound according to claim 6, wherein n is 0 and X is C_2-C_{10}-alkyl.

8. Compound according to claim 1 or 2, wherein m=2 and R_3 is –O-phenyl, wherein the phenyl residue is optionally substituted by one or more groups chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, halogen, C_2-C_6-alkenyl, halo-(C_1-C_6)-alkyl, halo-(C_1-C_6)-alkoxy, phenyl, phenyl(C_1-C_6)-alkyl, phenoxy, C_1-C_6-alkylcarbonyl, phenylcarbonyl, phenyl(C_1-C_6)alkylcarbonyl, C_1-C_6-alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, C_1-C_6-alkylcarbonylamino, hydroxy, cyano, nitro, amino, N-(C_1-C_6)-alkylamino, N,N-(C_1-C_6)-dialkylamino, carboxy, sulfo, sulfamoyl, sulfonylamino, (C_1-C_6)alkylaminosulfonyl or (C_1-C_6)alkylsulfonylamino; or wherein the phenyl ring is substituted by two neighbouring residues, which together with the phenyl ring to which they are attached form tetrahydronaphthyl.

9. Compound according to claim 8, wherein the phenyl group is optionally substituted by one or more groups chosen from phenyl, C_1-C_6-alkoxycarbonyl,

C_1-C_6-alkylcarbonylamino, C_1-C_6-alkoxy, C_1-C_6-alkyl, halo-(C_1-C_6)-alkyl, or halogen or wherein the phenyl group is substituted by two neigbouring residues, which together with the phenyl group to which they are attached form tetrahydronaphthyl.

10. Compound according to claim 9, wherein the phenyl residue is optionally substituted by one or more groups chosen from methoxy, ethoxy, propoxy, isopropoxy, ethyl, propyl, isopropyl, bromide, trifluoromethyl, methylamide or ethoxycarbonyl.

11. Compound according to any of claims 8 to 10, wherein the phenyl group is substituted in *ortho*- and/or *meta*- position.

12. Compound according to any of claims 8 to 11, wherein R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5- or 6-membered ring; and R_4 is N.

13. Compound according to any of claims 8 to 12, wherein n is 0 and X is C_2-C_{10}-alkyl.

14. Compound according to any of claims 8 to 11, wherein R_1 is H and R_2 is absent and R_4 is S.

15. Compound according to claim 14, wherein n is 0 and X is C_2-C_{10}-alkyl.

16. Compound according to claims 1 or 2, wherein m is 1 and R_3 is 2-quinolyl.

17. Compound according to claim 16, wherein R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring; R_4 is N.

18. Compound according to any of claims 17 to 18, wherein n is 0; and X is C_2-C_{10}-alkyl.

19. Compound according to claim 1, wherein the compound is selected from:

(a) 2-[4-[(Chroman-2(*R*)-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-

c]imidazole;

(b) 2-[4-[(Chroman-2-yl)methylamino]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine;

(c) 2-[4-[(Chroman-2-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*a*]pyrazine;

(d) 2-[5-[(Chroman-2-yl)methylamino]pentyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(e) 2-[6-[(Chroman-2-yl)methylamino]hexyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(f) 2-[3-[(Chroman-2-yl)methylamino]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(g) 3-[8-[(Chroman-2-yl)methylamino]octyl]-2,4-dioxothiazolidine;

(h) 2-[4-[(Chroman-2(*S*)-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(i) 2-[8-[(Chroman-2-yl)methylamino]octyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(j) 2-[3-[[(Chroman-2-yl)methylamino]methyl]benzyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(k) 2-[4-[[(Chroman-2-yl)methylamino]methyl]benzyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(l) (*E*)-2-[4-[(Chroman-2-yl)methylamino]but-2-enyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(m) 2-[4-[2-(*o*-Methoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(n) 2-[4-[2-(*m*-Methoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(o) 2-[4-[2-(*o*-Bromophenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(p) 2-[4-[2-(*m*-Bromophenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(q) 2-[4-[2-(*o*-Ethylphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(r) 2-[4-[2-(*m*-Ethylphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(s) 2-[4-[2-(*o*-Isopropylphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(t) 2-[4-[(2-quinolyl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-

c]imidazole;

(u) 2-[4-[2-(*o*-Ethoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(v) 2-[4-[2-(*o*-Isopropoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(w) 2-[4-[2-[*m*-(Trifluoromethyl)phenoxy]ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(x) 2-[4-[2-(1,1'-Biphenyl-2-yloxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(y) 2-[4-[2-[*o*-(Acetylamino)phenoxy]ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(z) 2-[4-[2-[*m*-(Acetylamino)phenoxy]ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(aa) 2-[4-[2-[*o*-(Ethoxycarbonyl)phenoxy]ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(bb) 2-[4-[2-(5,6,7,8-Tetrahydronaphth-1-yloxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(cc) 2-[4-[2-(2,3-Dimethylphenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole;

(dd) 2-[4-[(Chroman-2-yl)methylamino]butyl]-1,4-dioxoperhydropyrido[1,2-*a*]pyrazine;

(ee) (*Z*)-2-[4-[(Chroman-2-yl)methylamino]but-2-enyl]-1,4-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(ff) 3-[4-[2-(o-Ethoxyphenoxy)ethylamino]butyl]-2,4-dioxothiazolidine;

(gg) 3-[6-[2-(*o*-Ethoxyphenoxy)ethylamino]hexyl]-2,4-dioxothiazolidine;

(hh) 3-[8-[2-(*o*-Ethoxyphenoxy)ethylamino]octyl]-2,4-dioxothiazolidine;

(ii) 2-[4-[2-(*o*-Ethoxyphenoxy)ethylamino]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine;

(jj) 2-[6-[2-(*o*-Ethoxyphenoxy)ethylamino]hexyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine;

(kk) 2-[4-[(2-Quinolyl)methylamino]butyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine;

(ll) 2-[6-[(2-Quinolyl)methylamino]hexyl]-1,3-dioxoperhydroimidazo[1,5-*a*]pyridine;

a pharmaceutically acceptable salt or one of their stereochemically isomer forms.

20. Pharmaceutical composition which comprises a therapeutically effective amount of a compound as claimed in any of claims 1 to 19 and, pharmaceutically acceptable carriers.

21. Use of a compound of any of claims 1 to 19 for the preparation of a medicament for the treatment and/or prophylasis of pathological states in which 5-HT_{1A} agonists are indicated.

22. The use according to claim 21 in the preparation of a medicament for the treatment and/or prophylasis of Parkinson Disease, cerebral damage by thromboembolic ictus, craneoencephalic traumatisms, depression, migraine, pain, psychosis, anxiety disorders, aggressive disorders or urinary tract disorders.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/000840

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 C07D417/12 C07D417/04 C07D277/34 A61K31/4188 A61K31/427

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/29687 A (JANSSEN PHARMACEUTICA N.V; WIGERINCK, PIET, TOM, BERT, PAUL; VERSCHUER) 17 June 1999 (1999-06-17) tables F-3; compound 73	1-3,5,20
A	WO 03/029250 A (BAYER AKTIENGESELLSCHAFT; SCHERLING, DIETRICH; KARL, WOLFGANG; SEIDEL,) 10 April 2003 (2003-04-10) page 1, line 18 - page 2, line 3	1-22
A	EP 0 352 613 A (BAYER AG) 31 January 1990 (1990-01-31) page 2, line 9 - page 6, line 1	1-22

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2005	27/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Usuelli, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/000840

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/014915 A (CEPA SCHWARZ PHARMA S.L; DEL RIO ZAMBRANA, JOAQUIN; FRECHILLA MANSO, D) 19 February 2004 (2004-02-19) page 1, line 1 - page 1, line 22 page 3, line 18 - page 4, line 32; example all -----	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/000840

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9929687	A	17-06-1999	AU	748669 B2	06-06-2002
			AU	2412799 A	28-06-1999
			BG	104372 A	29-12-2000
			BR	9814256 A	03-10-2000
			CA	2311669 A1	17-06-1999
			CN	1280577 A ,C	17-01-2001
			EA	3365 B1	24-04-2003
			EE	200000328 A	15-08-2001
			WO	9929687 A1	17-06-1999
			EP	1036073 A1	20-09-2000
			HR	20000340 A1	30-04-2001
			HU	0004492 A2	28-03-2002
			ID	24616 A	27-07-2000
			IL	136529 A	12-03-2003
			JP	2001525407 T	11-12-2001
			NO	20002074 A	02-06-2000
			NZ	503603 A	26-10-2001
			PL	341007 A1	12-03-2001
			SK	8032000 A3	12-02-2001
			TR	200001542 T2	22-01-2001
			TW	577886 B	01-03-2004
			UA	70308 C2	15-11-2000
			US	2003083365 A1	01-05-2003
			US	6133277 A	17-10-2000
			US	2003149093 A1	07-08-2003
			US	6495547 B1	17-12-2002
			ZA	9811081 A	22-06-2000
WO 03029250	A	10-04-2003	DE	10148425 A1	17-04-2003
			CA	2462142 A1	10-04-2003
			WO	03029250 A1	10-04-2003
			EP	1434777 A1	07-07-2004
			JP	2005507901 T	24-03-2005
			US	2004259924 A1	23-12-2004
EP 0352613	A	31-01-1990	DE	3901814 A1	01-02-1990
			AT	104668 T	15-05-1994
			AU	627478 B2	27-08-1992
			AU	3898989 A	01-02-1990
			CA	1341162 C	02-01-2001
			CN	1039809 A ,C	21-02-1990
			DD	287500 A5	28-02-1991
			DE	58907493 D1	26-05-1994
			DK	371389 A	29-01-1990
			EP	0352613 A2	31-01-1990
			ES	2052829 T3	16-07-1994
			FI	893571 A ,B,	29-01-1990
			HK	38695 A	24-03-1995
			HU	58036 A2	28-01-1992
			HU	211160 B3	30-10-1995
			IE	62704 B1	22-02-1995
			IL	91126 A	30-03-1995
			JP	2096552 A	09-04-1990
			JP	2963107 B2	12-10-1999
			KR	183006 B1	01-05-1999
			NO	892892 A ,B,	29-01-1990
			NZ	230071 A	26-03-1992
			PT	91299 A ,B	08-02-1990

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/000840

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0352613 A		SG 12595 G	16-06-1995
		US 5506246 A	09-04-1996
		US 5137901 A	11-08-1992
		US 5585392 A	17-12-1996
		US 5300523 A	05-04-1994
		ZA 8905713 A	25-04-1990
WO 2004014915 A	19-02-2004	ES 2199086 A1	01-02-2004
		AU 2003254512 A1	25-02-2004
		CA 2492837 A1	19-02-2004
		WO 2004014915 A1	19-02-2004